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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07C 243/18, C07D 209/04, A61K 31/15, 31/40</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/01423</b>
			<b>(43) International Publication Date:</b> 14 January 1999 (14.01.99)
<b>(21) International Application Number:</b> PCT/DK98/00287			<b>KUKI, Atsuo [US/US];</b> 1603 Hawk View Drive, Encinitas, CA 92024 (US). <b>SHI, Shenghua [US/US];</b> 11693 Spring-side Road, San Diego, CA 92128 (US). <b>NAERUM, Lars [DK/DK];</b> Alrunevej 14, DK-2900 Hellerup (DK). <b>MADSEN, Peter [DK/DK];</b> Ulvejbjerg 7, DK-2880 Bagsværd (DK). <b>LAU, Jesper [DK/DK];</b> Rosenvangenget 3, DK-3520 Farum (DK). <b>PLEWE, Michael, Bruno [DE/US];</b> 8560 Via Mallorca, La Jolla, CA 92037 (US). <b>FENG, Jun [CN/US];</b> 8515 Chloe Avenue, La Mesa, CA 91942 (US). <b>JOHNSON, Michael, David [US/US];</b> 1968 Hanford Drive, San Diego, CA 92111 (US). <b>TESTON, Kimberly, Ann [US/US];</b> 3021 1/2 Oliphant Street, San Diego, CA 92106 (US). <b>SIDELMANN, Ulla, Grove [DK/DK];</b> Dronningeengen 10 A, DK-2950 Vedbæk (DK). <b>KNUDSEN, Lotte, Bjerre [DK/DK];</b> Valby Langgade 49A, 1tv, DK-2500 Valby (DK).
<b>(22) International Filing Date:</b> 1 July 1998 (01.07.98)			
<b>(30) Priority Data:</b> 08/886,785 1 July 1997 (01.07.97) US 09/032,516 27 February 1998 (27.02.98) US			
<b>(71) Applicants (for all designated States except US):</b> NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). <b>ALANEX CORPORATION [US/US];</b> 3350 General Atomics Court, San Diego, CA 92121 (US).			
<b>(71)(72) Applicants and Inventors:</b> <b>GONZALES, Javier [US/US];</b> 3998 Brown Street, Oceanside, CA 92056 (US). <b>SAMS, Christian [DK/DK];</b> Jakob Dannefaerds Vej 4a 1, DK-1973 Frederiksberg C (DK). <b>TENG, Min [CN/US];</b> 5185 Seachase Street, San Diego, CA 92130 (US).			
<b>(72) Inventors; and</b>			<b>(74) Common Representative:</b> NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).
<b>(75) Inventors/Applicants (for US only):</b> <b>LING, Anthony [US/US];</b> 10933 Caminito Cuesta, San Diego, CA 92131 (US). <b>GREGOR, Vlad [US/US];</b> 2711 Caminito Verdugo, Del Mar, CA 92014 (US). <b>HONG, Yufeng [CN/US];</b> 11980 Ashley Place, San Diego, CA 92128 (US). <b>KIEL, Dan [US/US];</b> 11367 Alvarez Meadow Court, San Diego, CA 92126 (US).			
			<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
			<b>Published</b> With international search report. With amended claims and statement.
<b>(54) Title:</b> GLUCAGON ANTAGONISTS/INVERSE AGONISTS			
<b>(57) Abstract</b>  Non-peptide compounds comprising a central hydrazide motif and methods for the synthesis thereof. The compounds act to antagonize the action of the glucagon peptide hormone.			

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## GLUCAGON ANTAGONISTS/INVERSE AGONISTS

### Field of the invention

- 5 The present invention relates to agents that act to antagonize the action of the glucagon peptide hormone. It relates particularly to non-peptide glucagon antagonists or inverse agonists.

### Background of the invention

- 10 Glucagon is a key hormonal agent that, in cooperation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (mostly liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposed by insulin which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones.
- 15 Glucagon is produced in the alpha islet cells and insulin in the beta islet cells of the pancreas. Diabetes mellitus, the common disorder of glucose metabolism, is characterized by hyperglycemia, and can present as type I, insulin-dependent, or type II, a form that is non-insulin-dependent in character. Subjects with type I diabetes are hyperglycemic and hypoinsulinemic,
- 20 and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with type I or II diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy animals as well as in animal models of type I and II, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level (Brand et al. Diabetologia 37, 985 (1994);
- 25 Diabetes 43, [suppl 1], 172A (1994); Am J Physiol 269, E469-E477 (1995); Diabetes 44 [suppl 1], 134A (1995); Diabetes 45, 1076 (1996)). These studies suggest that glucagon suppression or an action antagonistic to glucagon could be a useful adjunct to conventional antihyperglycemia treatment of diabetes. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, substances that inhibit or prevent glucagon induced response.
- 30 The antagonist can be peptide or non-peptide in nature. Native glucagon is a 29 amino acid-containing peptide having the sequence:

His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-NH<sub>2</sub>.

- 5    Glucagon exerts its action by binding to and activating its receptor, which is part of the Glucagon-Secretin branch of the 7-transmembrane G-protein coupled receptor family (Jelinek et al. Science 259, 1614, (1993)). The receptor functions by activation of the adenylyl cyclase second messenger system and the result is an increase in cAMP levels.
- 10   Several publications disclose peptide antagonists. Probably, the most thoroughly characterized antagonist is DesHis<sup>1</sup>[Glu<sup>9</sup>]-glucagon amide (Unson et al., Peptides 10, 1171 (1989); Post et al., Proc. Natl. Acad. Sci. USA 90, 1662 (1993)). Other antagonists are eg DesHis<sup>1</sup>,Phe<sup>6</sup>[Glu<sup>9</sup>]-glucagon amide (Azizh et al., Bioorganic & Medicinal Chem. Lett. 16, 1849 (1995)) or NLeu<sup>9</sup>,Ala<sup>11,16</sup>-glucagon amide (Unson et al., J. Biol. Chem. 269(17), 12548
- 15   (1994)).

- Peptide antagonists of peptide hormones are often quite potent; however, they are defective as drugs because of degradation by physiological enzymes, and poor biodistribution. Therefore, non-peptide antagonists of the peptide hormones are preferred. Among the non-peptide glucagon antagonists, a quinoxaline derivative, (2-styryl-3-[3-(dimethylamino)propylmethyl-
- 20   amino]-6,7-dichloroquinoxaline was found to displace glucagon from the rat liver receptor (Collins, J.L. et al. (1992) Bioorganic and Medicinal Chemistry Letters 2(9):915-918). West, R.R. et al. (1994), WO 94/14426 discloses use of skyrin, a natural product comprising a pair of linked 9,10-anthracenedione groups, and its synthetic analogues, as glucagon antagonists.
- 25   Anderson, P.L., U.S. Patent No. 4,359,474 discloses the glucagon antagonistic properties of 1-phenyl pyrazole derivatives. Barcza, S., U.S. Patent No. 4,374,130, discloses substituted disilacyclohexanes as glucagon antagonists. WO 98/04528 (Bayer Corporation) discloses substituted pyridines and biphenyls as glucagon antagonists. Furthermore, WO 97/16442 (Merck & Co., Inc.) discloses substituted pyridyl pyrroles as glucagon antagonists and WO 98/21957
- 30   (Merck & Co., Inc.) discloses 2,4-diaryl-5-pyridylimidazoles as glucagon antagonists. These glucagon antagonists differ structurally from the present compounds.

## Description of the invention

### Definitions

The following is a detailed definition of the terms used to describe the compounds of the invention:

5

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

The term "alkyl" in the present context designates a hydrocarbon chain or a ring that is either saturated or unsaturated (containing one or more double or triple bonds where feasible) of from 1 to 10 carbon atoms in either a linear or branched or cyclic configuration. Thus, alkyl includes for example n-octyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, allyl, propargyl, 2-hexynyl, cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, cyclooctyl, 4-cyclohexylbutyl, and the like.

Further non-limiting examples are *sec*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl, n-heptyl, n-nonyl, n-decyl, vinyl, 1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 2,4-heptadienyl, 1-octenyl, 2,4-octadienyl, ethynyl, 1-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 2-decynyl, cyclobutyl, cyclopentyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclohexenylmethyl, 4-cyclohexyl-2-butenyl, 4-(1-cyclohexenyl)-vinyl and the like.

25

The term "lower alkyl" designates a hydrocarbon moiety specified above, of from 1 to 6 carbon atoms.

"Aryl" means an aromatic ring moiety, for example: phenyl, naphthyl, furyl, thienyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazolyl, imidazolyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,

30

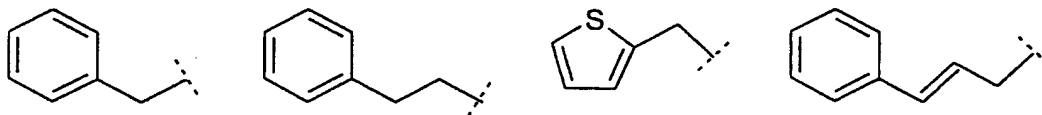
1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, isothiazolyl, tetrazolyl, 1-H-tetrazol-5-yl, indolyl, quinolyl, quinazolinyl, benzofuryl, benzothiophenyl (thianaphthenyl) and the like.

Further non-limiting examples are biphenyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, 1,2,3,4-tetrahydronaphthyl, 2,3-dihydrobenzofuryl, triazolyl, pyranlyl, thiadiazinyl, isoindolyl, indazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinoliziny, isoquinolyl, quinoxaliny, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, pyrrolinyl, pyrazolinyl, indolinyl, pyrrolidinyl, piperidinyl and the like.

The aryl moieties are optionally substituted by one or more substituents, for example selected from the group consisting of F, Cl, I, and Br; lower alkyl; lower alkanoyl such as formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the like; -OH; -NO<sub>2</sub>; -CN; -CO<sub>2</sub>H; -O-lower alkyl; aryl; aryl-lower alkyl; -CO<sub>2</sub>CH<sub>3</sub>; -CONH<sub>2</sub>; -OCH<sub>2</sub>CONH<sub>2</sub>; -NH<sub>2</sub>; -N(CH<sub>3</sub>)<sub>2</sub>; -SO<sub>2</sub>NH<sub>2</sub>; -OCHF<sub>2</sub>; -CF<sub>3</sub>; -OCF<sub>3</sub> and the like. A further non-limiting example is -NH-(C=S)-NH<sub>2</sub>.

Such aryl moieties may also be substituted by two substituents forming a bridge, for example -OCH<sub>2</sub>O-.

"Aryl-lower alkyl" means a lower alkyl as defined above, substituted by an aryl, for example:

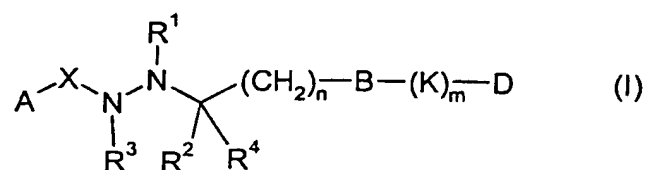


The aryl group is optionally substituted as described above.

#### Description of the invention

The present invention is based on the unexpected observation that compounds having a selected nitrogen-bearing central motif and the general structural features disclosed below antagonize the action of glucagon.

Accordingly, the invention is concerned with compounds of the general formula I:



5

wherein:

R<sup>1</sup> and R<sup>2</sup> independently are hydrogen or lower alkyl or together form a valence bond;

10 R<sup>3</sup> and R<sup>4</sup> independently are hydrogen or lower alkyl;

n is 0, 1, 2 or 3;

m is 0 or 1;

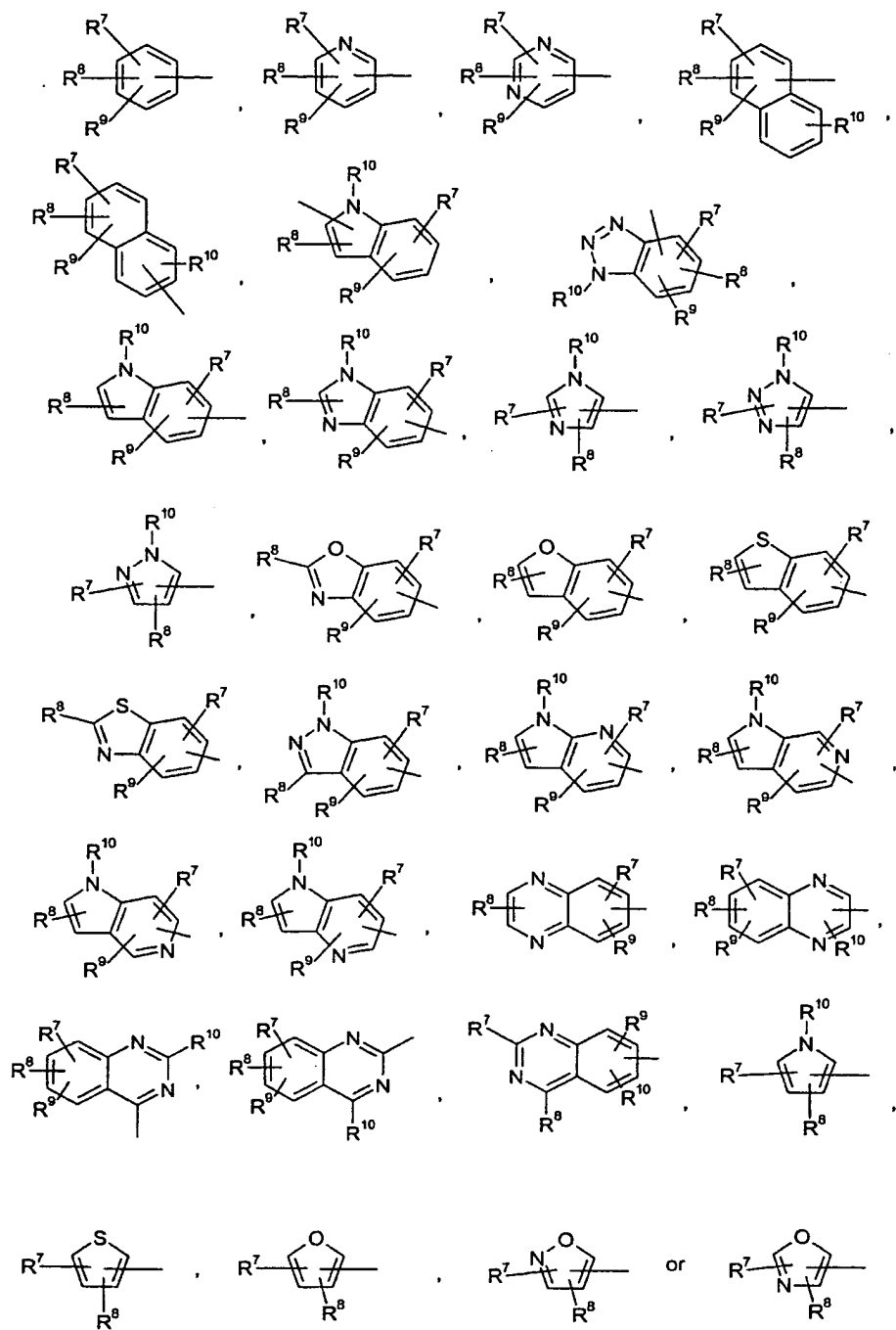
15

X is >C=O, >C=S, >C=NR<sup>5</sup> or >SO<sub>2</sub>;

wherein R<sup>5</sup> is hydrogen, lower alkyl, aryl-lower alkyl or -OR<sup>6</sup>;

20 wherein R<sup>6</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

A is



wherein:

$R^7$  is hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -OCH<sub>2</sub>CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup> or -OSO<sub>2</sub>CF<sub>3</sub>;

- 5  $R^8$  and  $R^9$  independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, -SCF<sub>3</sub>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup> or -OSO<sub>2</sub>CF<sub>3</sub>, or  $R^8$  and  $R^9$  together form a bridge -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;

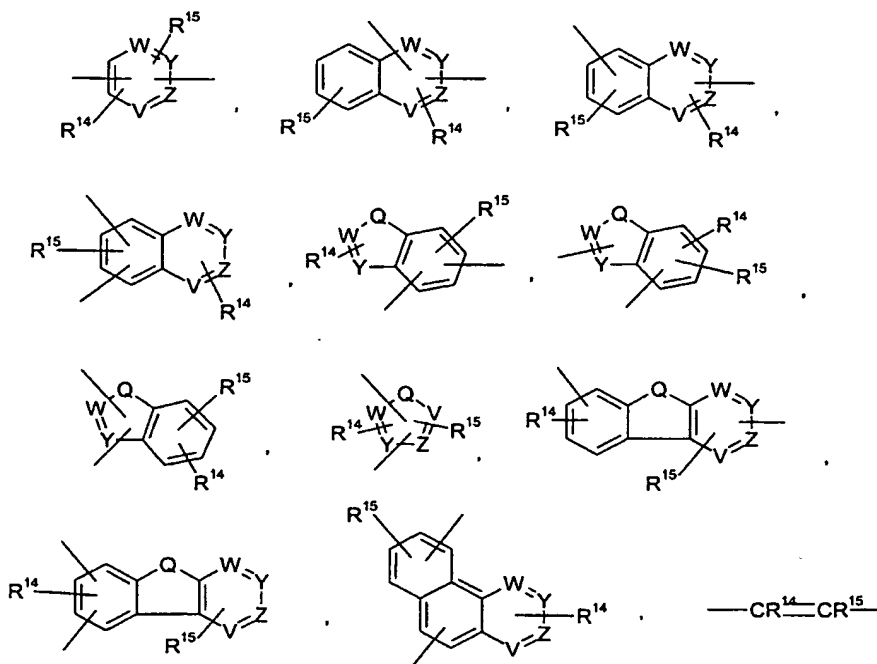
- 10 wherein  $R^{11}$  and  $R^{12}$  independently are hydrogen, -COR<sup>13</sup>, -SO<sub>2</sub>R<sup>13</sup>, lower alkyl or aryl;

wherein  $R^{13}$  is hydrogen, lower alkyl, aryl-lower alkyl or aryl; and

$R^{10}$  is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

15

B is



or a valence bond;

wherein:

R<sup>14</sup> and R<sup>15</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -O(CH<sub>2</sub>)<sub>l</sub>CF<sub>3</sub>, -NO<sub>2</sub>,  
 -OR<sup>16</sup>, -NR<sup>18</sup>R<sup>17</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>16</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 5 -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>16</sup>R<sup>17</sup>, -(CH<sub>2</sub>)<sub>l</sub>CONR<sup>16</sup>R<sup>17</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CONR<sup>16</sup>R<sup>17</sup>, -(CH<sub>2</sub>)<sub>l</sub>COR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>COR<sup>16</sup>,  
 -(CH<sub>2</sub>)<sub>l</sub>OR<sup>16</sup>, -O(CH<sub>2</sub>)<sub>l</sub>OR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>NR<sup>16</sup>R<sup>17</sup>, -O(CH<sub>2</sub>)<sub>l</sub>NR<sup>16</sup>R<sup>17</sup>, -OCOR<sup>16</sup>, -CO<sub>2</sub>R<sup>18</sup>,  
 -O(CH<sub>2</sub>)<sub>l</sub>CO<sub>2</sub>R<sup>18</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CN, -O(CH<sub>2</sub>)<sub>l</sub>Cl, or R<sup>14</sup> and R<sup>15</sup> together form a bridge -O(CH<sub>2</sub>)<sub>l</sub>O- or  
 -(CH<sub>2</sub>)<sub>l</sub>;

10 wherein l is 1, 2, 3 or 4;

R<sup>16</sup> and R<sup>17</sup> independently are hydrogen, -COR<sup>18</sup>, -SO<sub>2</sub>R<sup>18</sup>, lower alkyl, aryl, or R<sup>16</sup> and R<sup>17</sup>  
 together form a cyclic alkyl bridge containing from 2 to 7 carbon atoms;

15 wherein R<sup>18</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

W is -N= or -CR<sup>19</sup>=;

Y is -N= or -CR<sup>20</sup>=;

20

Z is -N= or -CR<sup>21</sup>=;

V is -N= or -CR<sup>22</sup>=; and

25 Q is -NR<sup>23</sup>-, -O- or -S-;

wherein:

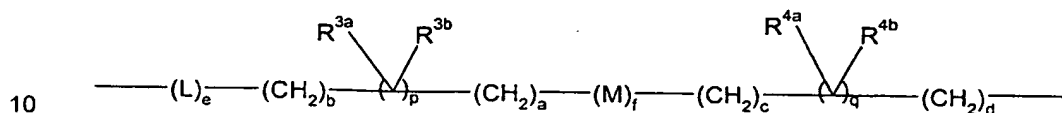
R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>,  
 30 -NO<sub>2</sub>, -OR<sup>24</sup>, -NR<sup>24</sup>R<sup>25</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>24</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>,  
 -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -OCH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>OR<sup>24</sup>,  
 -CH<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, -OCOR<sup>24</sup> or -CO<sub>2</sub>R<sup>24</sup>, or R<sup>19</sup> and R<sup>20</sup>, R<sup>20</sup> and R<sup>21</sup>, or R<sup>21</sup> and R<sup>22</sup> together form a  
 bridge -OCH<sub>2</sub>O-;

wherein  $R^{24}$  and  $R^{25}$  independently are hydrogen,  $-\text{COR}^{26}$ ,  $-\text{SO}_2\text{R}^{26}$ , lower alkyl, aryl or aryl-lower alkyl;

5 wherein  $R^{26}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

$R^{23}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



wherein:

15  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$  and  $R^{4b}$  independently are hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^{24a}$ ,  $-\text{NR}^{24a}\text{R}^{25a}$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{SCF}_3$ ,  $-\text{SR}^{24a}$ ,  $-\text{CHF}_2$ ,  $-\text{OCHF}_2$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{OSO}_2\text{CF}_3$ ,  $-\text{CONR}^{24a}\text{R}^{25a}$ ,  $-\text{CH}_2\text{CONR}^{24a}\text{R}^{25a}$ ,  $-\text{OCH}_2\text{CONR}^{24a}\text{R}^{25a}$ ,  $-\text{CH}_2\text{OR}^{24a}$ ,  $-\text{CH}_2\text{NR}^{24a}\text{R}^{25a}$ ,  $-\text{OCOR}^{24a}$  or  $-\text{CO}_2\text{R}^{24a}$ ;

20 wherein  $R^{24a}$  and  $R^{25a}$  independently are hydrogen,  $-\text{COR}^{26a}$ ,  $-\text{SO}_2\text{R}^{26a}$ , lower alkyl, aryl or aryl-lower alkyl;

wherein  $R^{26a}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

or

25

$R^{3a}$  and  $R^{3b}$ ,  $R^{4a}$  and  $R^{4b}$ , or  $R^{3a}$  and  $R^{4b}$  together form a bridge  $-(\text{CH}_2)_i\text{---}$ ;

wherein  $i$  is 1, 2, 3 or 4;

30 a, b, c and d independently are 0, 1, 2, 3 or 4;

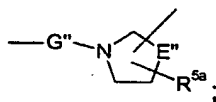
e, f and p independently are 0 or 1;

q is 0, 1 or 2; and

5 L and M independently are

-O-, -S-, -CH=CH-, -C≡C-, -NR<sup>5a</sup>-, -CH<sub>2</sub>NR<sup>5a</sup>-, -CO-, -OCO-, -COO-, -CONR<sup>5a</sup>-, -CONR<sup>5b</sup>-,  
 -NR<sup>5a</sup>CO-, -SO-, -SO<sub>2</sub>-, -OSO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>5a</sup>-, -NR<sup>5a</sup>SO<sub>2</sub>-, -NR<sup>5a</sup>CONR<sup>5b</sup>-, -CONR<sup>5a</sup>NR<sup>5b</sup>-,  
 -NR<sup>5a</sup>CSNR<sup>5b</sup>-, -OCONR<sup>5b</sup>-, -CH<sub>2</sub>CONR<sup>5b</sup>-, -OCH<sub>2</sub>CONR<sup>5b</sup>-,

-P(O)(OR<sup>5a</sup>)O-, -NR<sup>5a</sup>C(O)O- or



10

wherein R<sup>5a</sup> and R<sup>5b</sup> independently are hydrogen, lower alkyl, -OH, -(CH<sub>2</sub>)<sub>k</sub>-OR<sup>6a</sup>, -COR<sup>6a</sup>,  
 -(CH<sub>2</sub>)<sub>k</sub>-CH(OR<sup>6a</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>k</sub>-CN, -(CH<sub>2</sub>)<sub>k</sub>-NR<sup>6a</sup>R<sup>6b</sup>, aryl, aryl-lower alkyl, -(CH<sub>2</sub>)<sub>g</sub>-COOR<sup>43</sup> or -  
 (CH<sub>2</sub>)<sub>g</sub>-CF<sub>3</sub>;

15 wherein k is 1, 2, 3 or 4;

R<sup>6a</sup> and R<sup>6b</sup> independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl;

g is 0, 1, 2, 3 or 4;

20

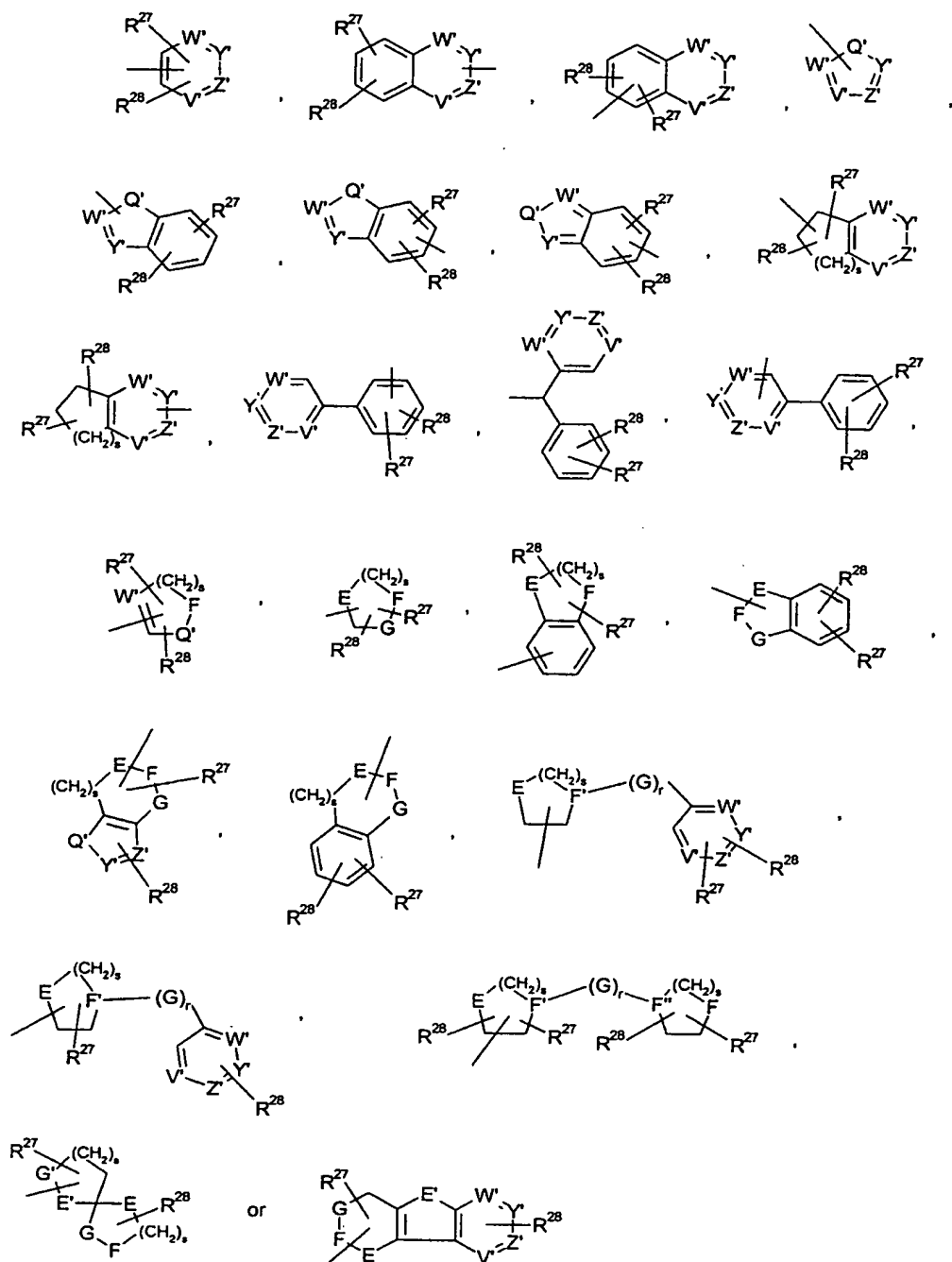
R<sup>43</sup> is hydrogen or lower alkyl;

G'' is -OCH<sub>2</sub>CO-, -CH<sub>2</sub>CO-, -CO- or a valence bond; and

25

E'' is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH=CH-, -CH<sub>2</sub>NH- or -CH<sub>2</sub>CH<sub>2</sub>NH-;

D is hydrogen,



wherein:

5

$r$  is 0 or 1;

s is 0, 1, 2 or 3;

E, E', F, G and G' independently are  $-\text{CHR}^{38}-$ ,  $>\text{C}=\text{O}$ ,  $>\text{NR}^{39}$ ,  $-\text{O}-$  or  $-\text{S}-$ ;

5

F' is  $>\text{CR}^{38}-$  or  $>\text{N}-$ ;

Y' is  $-\text{N}=\text{}$  or  $-\text{CR}^{32}=\text{}$ ;

10

Z' is  $-\text{N}=\text{}$  or  $-\text{CR}^{33}=\text{}$ ;

V' is  $-\text{N}=\text{}$  or  $-\text{CR}^{34}=\text{}$ ;

W' is  $-\text{N}=\text{}$  or  $-\text{CR}^{35}=\text{}$ ; and

15

Q' is  $-\text{NR}^{36}-$ ,  $-\text{O}-$  or  $-\text{S}-$ ;

wherein:

20

$\text{R}^{27}$ ,  $\text{R}^{28}$ ,  $\text{R}^{32}$ ,  $\text{R}^{33}$ ,  $\text{R}^{34}$  and  $\text{R}^{35}$  independently are hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{O}(\text{CH}_2)_y\text{CF}_3$ ,  $-(\text{CH}_2)_y\text{NHCOCF}_3$ ,  $-\text{NO}_2$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{SCF}_3$ ,  $-\text{SR}^{29}$ ,  $-\text{CHF}_2$ ,  $-\text{OCHF}_2$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{OSO}_2\text{R}^{29}$ ,  $-\text{OSO}_2\text{CF}_3$ ,  $-(\text{CH}_2)_y\text{CONR}^{29}\text{R}^{30}$ ,  $-\text{O}(\text{CH}_2)_y\text{CONR}^{29}\text{R}^{30}$ ,  $-(\text{CH}_2)_y\text{OR}^{29}$ ,  $-(\text{CH}_2)_y\text{NR}^{29}\text{R}^{30}$ ,  $-\text{OCOR}^{29}$ ,  $-\text{COR}^{29}$  or  $-\text{CO}_2\text{R}^{29}$ ;

25

or

$\text{R}^{27}$  and  $\text{R}^{28}$ ,  $\text{R}^{32}$  and  $\text{R}^{33}$ ,  $\text{R}^{33}$  and  $\text{R}^{34}$ , or  $\text{R}^{34}$  and  $\text{R}^{35}$  together form a bridge  $-\text{O}(\text{CH}_2)_y\text{O}-$ ;

wherein y is 0, 1, 2, 3 or 4; and

30

$\text{R}^{29}$  and  $\text{R}^{30}$  independently are hydrogen,  $-\text{COR}^{31}$ ,  $-\text{CO}_2\text{R}^{31}$ ,  $-\text{SO}_2\text{R}^{31}$ , lower alkyl, aryl or aryl-lower alkyl;

wherein  $R^{31}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

$R^{38}$  and  $R^{39}$  independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

- 5  $R^{38}$  is hydrogen,  $-OR^{40}$ ,  $-NR^{40}R^{41}$ , lower alkyl, aryl, aryl-lower alkyl,  $-SCF_3$ ,  $-SR^{40}$ ,  $-CHF_2$ ,  $-OCHF_2$ ,  $-OCF_2CHF_2$ ,  $-CONR^{40}R^{41}$ ,  $-(CH_2)_xCONR^{40}R^{41}$ ,  $-O(CH_2)_xCONR^{40}R^{41}$ ,  $-(CH_2)_xOR^{40}$ ,  $-(CH_2)_xNR^{40}R^{41}$ ,  $-OCOR^{40}$  or  $-CO_2R^{40}$ ;

wherein  $x$  is 1, 2, 3 or 4;

10

$R^{40}$  and  $R^{41}$  independently are hydrogen,  $-COR^{42}$ ,  $-SO_2R^{42}$ , lower alkyl, aryl or aryl-lower alkyl;

wherein  $R^{42}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

15

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

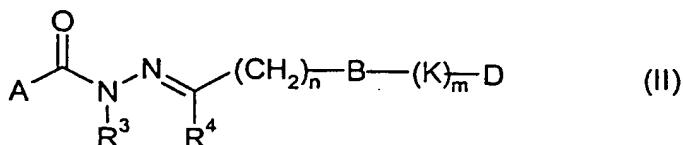
- Where the formulae for B make it possible,  $R^{19}$ ,  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$  and  $R^{23}$  may alternatively be replaced by  $R^{14}$  or  $R^{15}$ , respectively. In such case eg W may be selected from  $-N=$ ,  $-CR^{19}-$  and  $-CR^{14}-$ .

20

Similarly, where the formulae for D make it possible,  $R^{32}$ ,  $R^{33}$ ,  $R^{34}$ ,  $R^{35}$ ,  $R^{36}$ ,  $R^{38}$  and  $R^{39}$  may alternatively be replaced by  $R^{27}$  or  $R^{28}$ , respectively. In such case eg E may be selected from  $-CHR^{38}-$ ,  $>C=O$ ,  $>NR^{39}$ ,  $-O-$ ,  $-S-$ ,  $-CHR^{27}-$  and  $>NR^{27}$ .

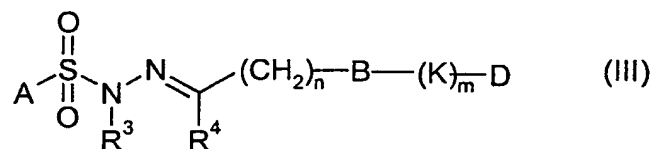
25

In a preferred embodiment the invention relates to compounds of the following general formula II:



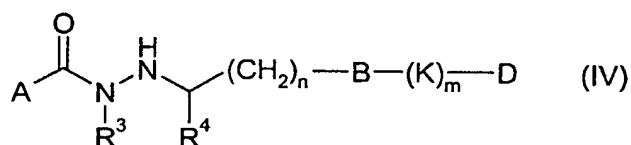
- 30 wherein A, B, K, D,  $R^3$ ,  $R^4$ ,  $n$  and  $m$  are as defined for formula I.

In another preferred embodiment the invention relates to compounds of the following general formula III:



5 wherein A, B, K, D, R<sup>3</sup>, R<sup>4</sup>, n and m are as defined for formula I.

In still another preferred embodiment the invention relates to compounds of the following formula IV:



10 wherein A, B, K, D, R<sup>3</sup>, R<sup>4</sup>, n and m are as defined for formula I.

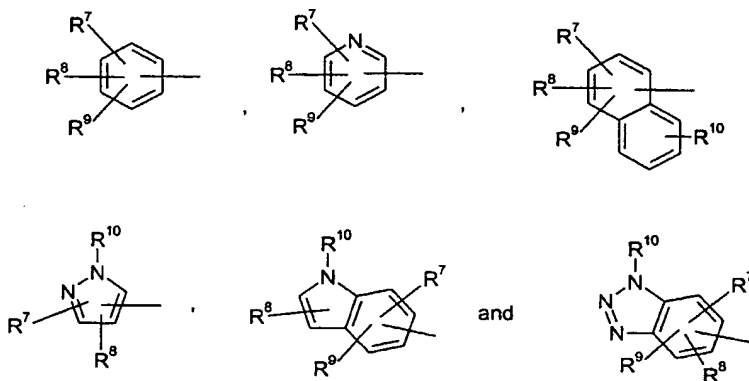
In the compounds of the above formulae I to IV the following substituents are preferred:

R<sup>3</sup> is preferably hydrogen.

15

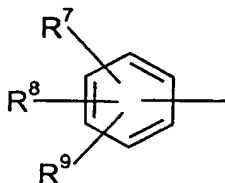
R<sup>4</sup> is preferably hydrogen.

A is preferably selected from the group consisting of:



wherein  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  are as defined for formula I.

A is more preferably



5 wherein  $R^7$ ,  $R^8$  and  $R^9$  are as defined for formula I.

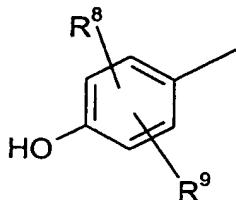
In the above embodiments of A,  $R^7$  is preferably halogen, lower alkyl, -OH, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, -O-lower alkyl, aryl, aryl-lower alkyl, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -OCH<sub>2</sub>CONH<sub>2</sub>, -NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -OCHF<sub>2</sub>, -CF<sub>3</sub> or -OCF<sub>3</sub>.

10

Preferably,  $R^8$  and  $R^9$  are independently hydrogen, halogen, -OH, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -OCF<sub>3</sub>, -SCF<sub>3</sub>, -CF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -O-lower alkyl such as methoxy and ethoxy, lower alkyl such as methyl and ethyl, or phenyl, and  $R^{10}$  is hydrogen, lower alkyl or phenyl.

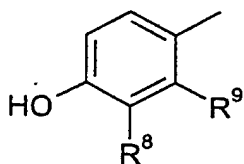
15 More preferably,  $R^8$  and  $R^9$  are independently selected from hydrogen, halogen such as -F and -Cl, -O-lower alkyl such as methoxy and ethoxy, -NH<sub>2</sub>, -CN or -NO<sub>2</sub>, and  $R^{10}$  is hydrogen.

In a particularly preferred embodiment A is



20 wherein  $R^8$  and  $R^9$  independently are hydrogen, halogen, -OH, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -OCF<sub>3</sub>, -SCF<sub>3</sub>, -CF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -O-lower alkyl such as methoxy and ethoxy, lower alkyl such as methyl and ethyl, or phenyl, preferably hydrogen, halogen such as -F and -Cl, -O-lower alkyl such as methoxy and ethoxy, -NH<sub>2</sub>, -CN or -NO<sub>2</sub>.

25 In a further particularly preferred embodiment A is

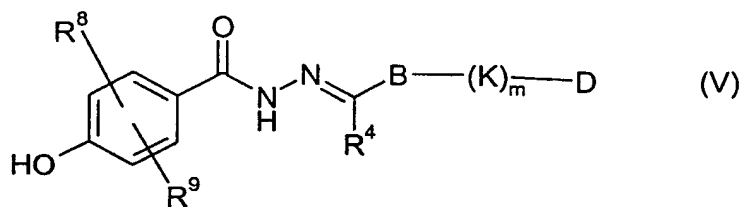


wherein  $R^8$  is hydrogen, halogen such as -F or -Cl, -O-lower alkyl such as  $-OCH_3$  or  $-OC_2H_5$ ,  $-NH_2$ , -CN or  $-NO_2$ ; and  $R^9$  is hydrogen or halogen such as -F or -Cl.

5

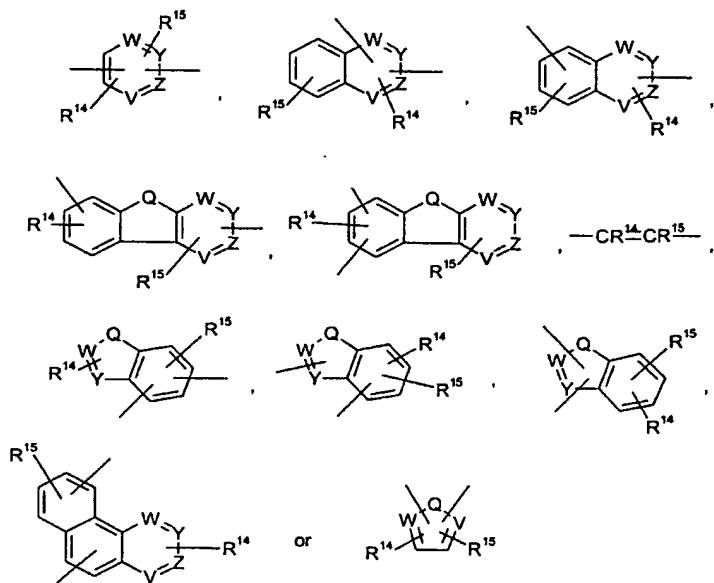
In a preferred embodiment  $R^8$  is halogen and  $R^9$  is hydrogen.

In still a preferred embodiment the invention relates to compounds of the following formula V:



10 wherein  $R^4$ , B, K, D and m are as defined for formula I and  $R^8$  and  $R^9$  are as defined for formula I and preferably as defined for the preferred embodiments of A above.

B is preferably:



wherein V, W, Z, Y and Q are as defined for formula I; and

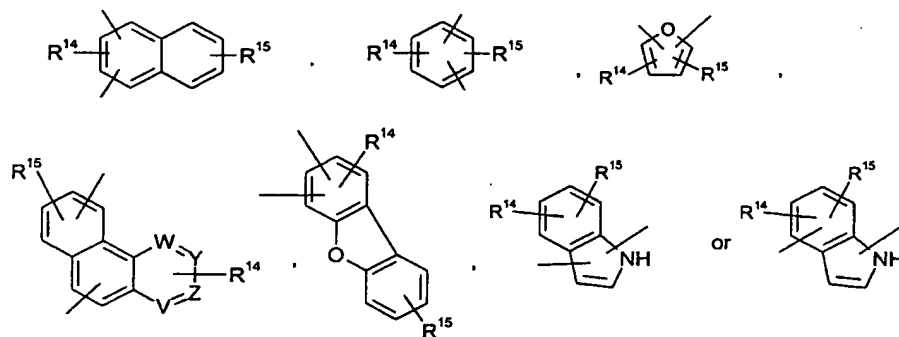
$R^{14}$  and  $R^{15}$  independently are hydrogen, halogen,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OR}^{16}$ ,  $-\text{NR}^{16}\text{R}^{17}$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{OSO}_2\text{CF}_3$ ,  $-\text{CONR}^{16}\text{R}^{17}$ ,  $-\text{CH}_2\text{OR}^{16}$ ,  $-\text{CH}_2\text{NR}^{16}\text{R}^{17}$ ,  $-\text{OCOR}^{16}$  or  $-\text{CO}_2\text{R}^{18}$ ;  
 5 or  $R^{14}$  and  $R^{15}$  together form a bridge  $-\text{OCH}_2\text{O}-$  or  $-(\text{CH}_2)_l-$ ;

wherein I,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are as defined for formula I.

Q is preferably  $-\text{O}-$  or  $-\text{NH}-$ .

10

Particularly preferred compounds are those in which B is



15 wherein V, W, Z, Y and Q are as defined for formula I; and

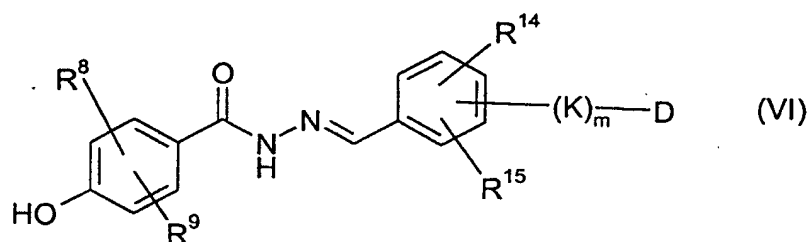
$R^{14}$  and  $R^{15}$  independently are hydrogen, halogen,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OR}^{16}$ ,  $-\text{NR}^{16}\text{R}^{17}$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{OSO}_2\text{CF}_3$ ,  $-\text{CONR}^{16}\text{R}^{17}$ ,  $-\text{CH}_2\text{OR}^{16}$ ,  $-\text{CH}_2\text{NR}^{16}\text{R}^{17}$ ,  $-\text{OCOR}^{16}$  or  $-\text{CO}_2\text{R}^{18}$ ;  
 20 or  $R^{14}$  and  $R^{15}$  together form a bridge  $-\text{OCH}_2\text{O}-$  or  $-(\text{CH}_2)_l-$ ;

20

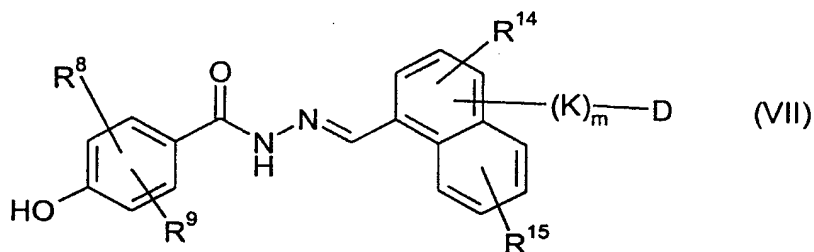
wherein I,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are as defined for formula I.

Still more preferred are compounds of the following formula VI:

18

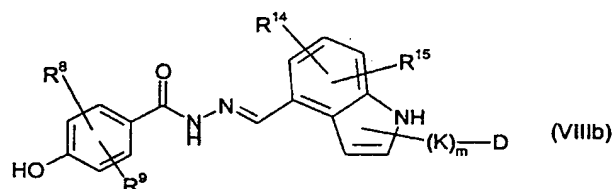
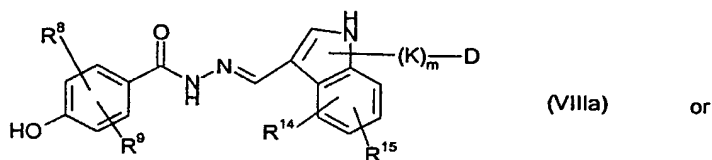


as well as compounds of the following formula VII:



5

as well as compounds of the general formulae VIIIa or VIIIb:



10

wherein  $R^{14}$  and  $R^{15}$  independently are hydrogen, halogen,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OR}^{16}$ ,  $-\text{NR}^{16}\text{R}^{17}$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{OSO}_2\text{CF}_3$ ,  $-\text{CONR}^{16}\text{R}^{17}$ ,  $-\text{CH}_2\text{OR}^{16}$ ,  $-\text{CH}_2\text{NR}^{16}\text{R}^{17}$ ,  $-\text{OCOR}^{16}$  or  $-\text{CO}_2\text{R}^{18}$ ; or  $R^{14}$  and  $R^{15}$  together form a bridge  $-\text{OCH}_2\text{O}-$  or  $-(\text{CH}_2)_n-$ ;

15      wherein I,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are as defined for formula I;

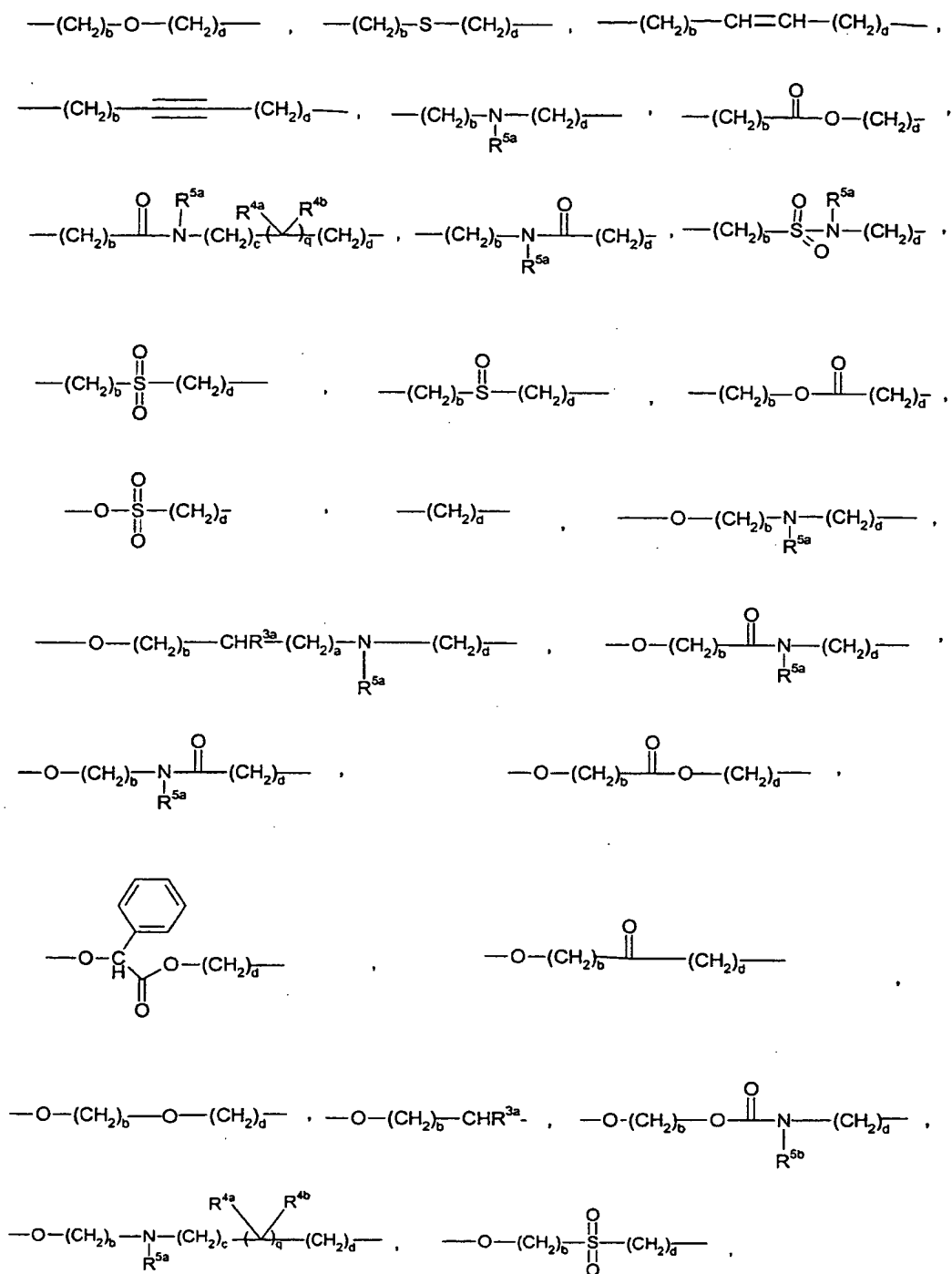
K, D and m are as defined for formula I; and

5 R<sup>8</sup> and R<sup>9</sup> are as defined for formula I and preferably as defined for the preferred embodiments of A above.

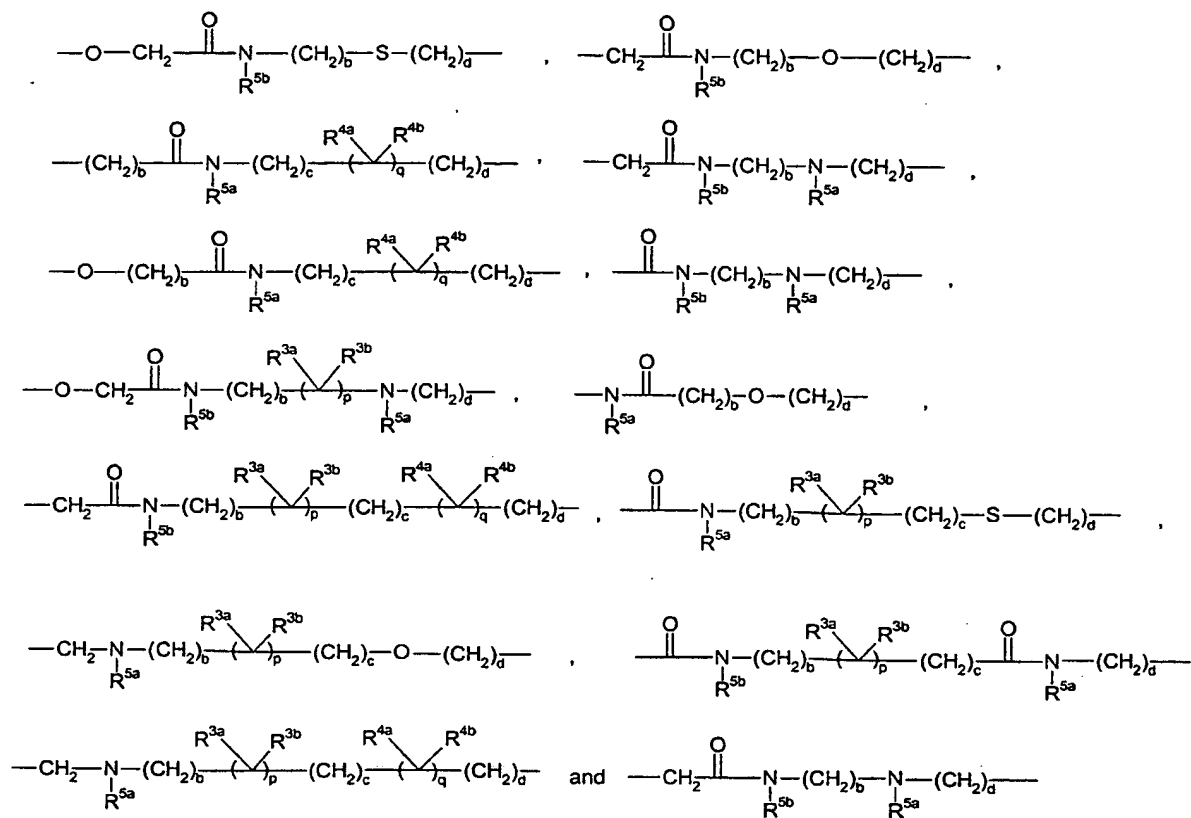
In the above formulae VI, VII and VIII, R<sup>14</sup> and R<sup>15</sup> are preferably independently hydrogen, halogen, lower alkyl, aryl such as phenyl, or -O-lower alkyl such as methoxy.

10 In the above formulae VI and VII, K is preferably bound in para-position and in the above formulae VIIIa and VIIIb, K is preferably bound at the nitrogen atom of the indole group.

K is preferably selected from the group consisting of:

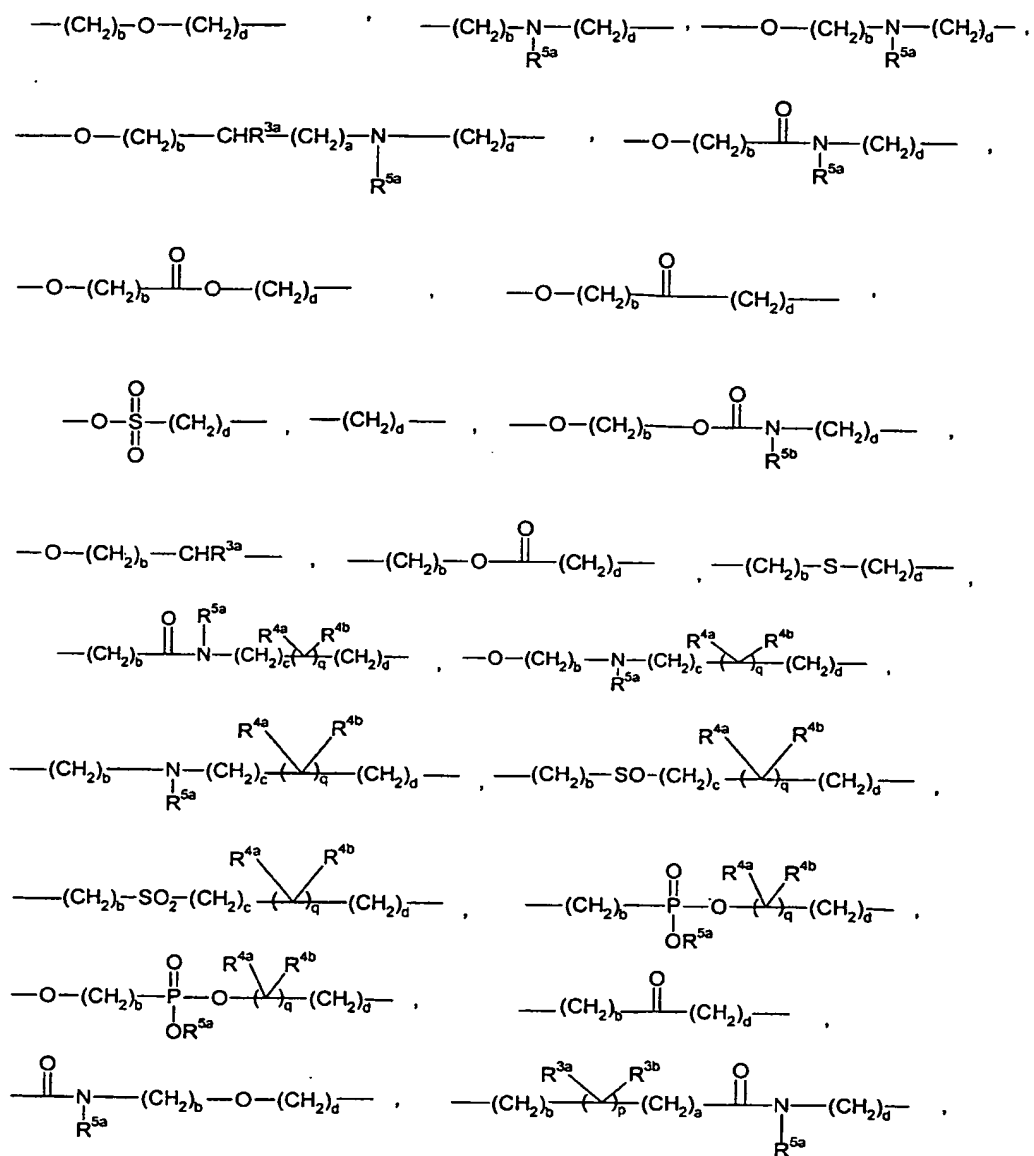


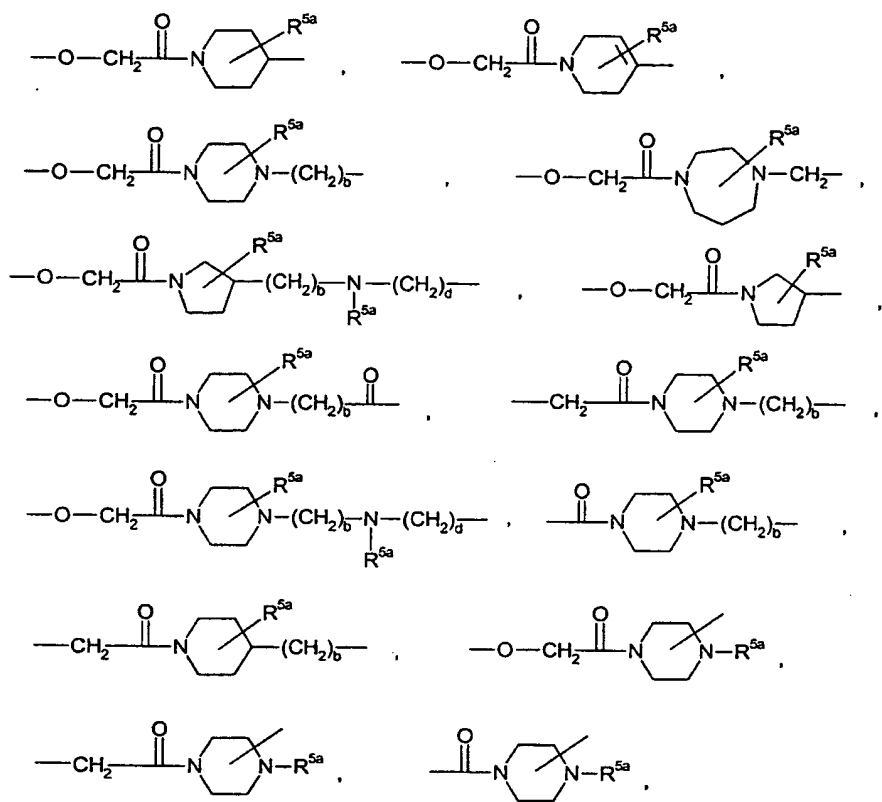


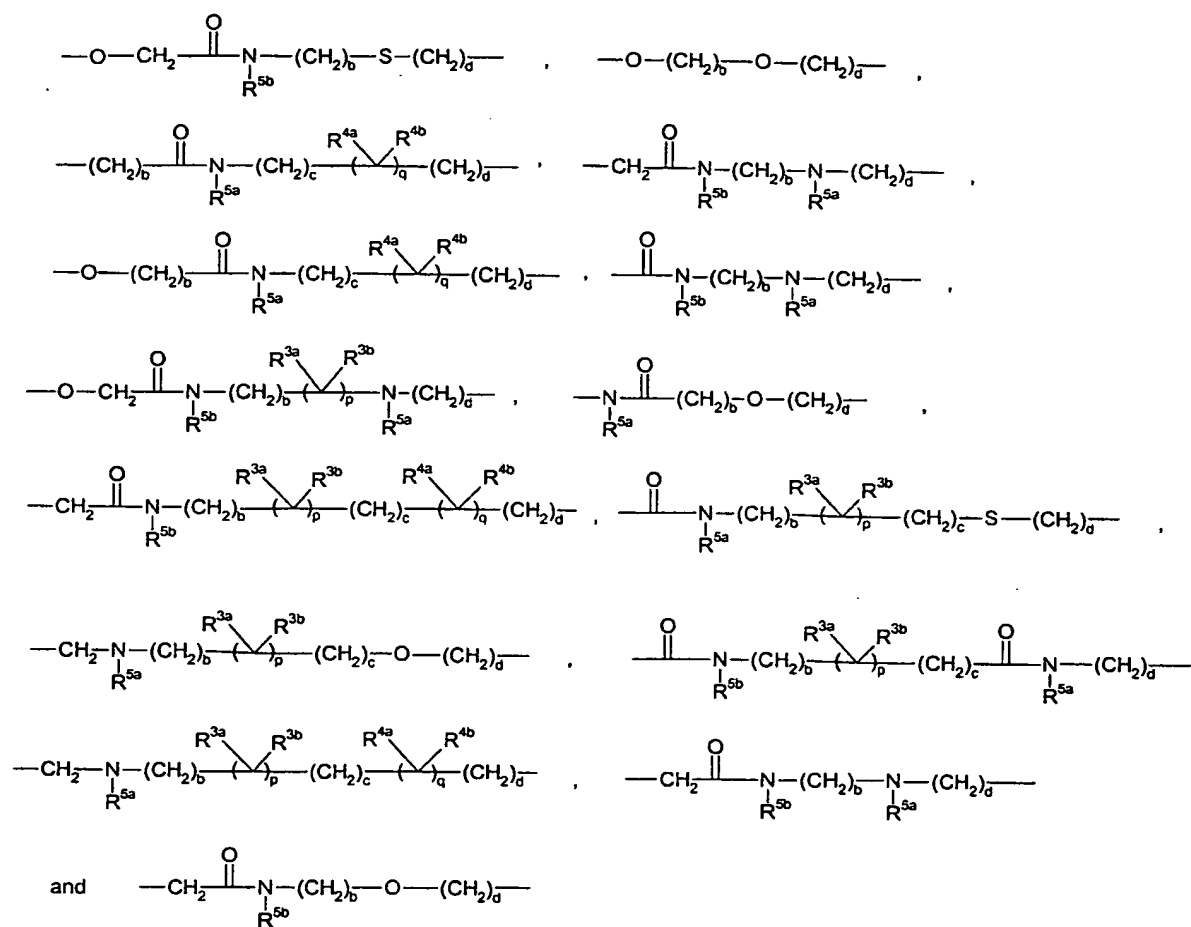


wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined for formula I.

- 5 More preferably, K is selected from the group consisting of:

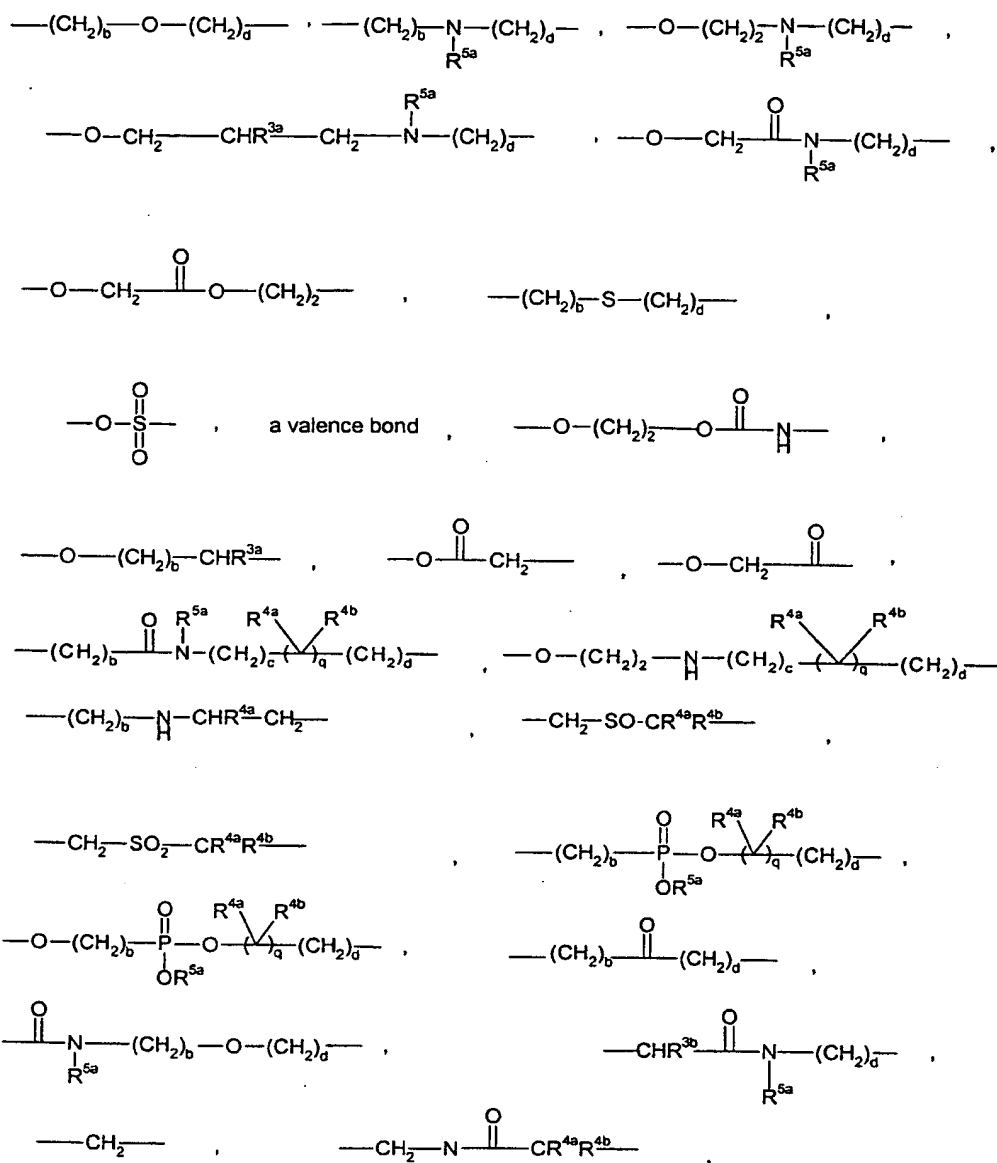


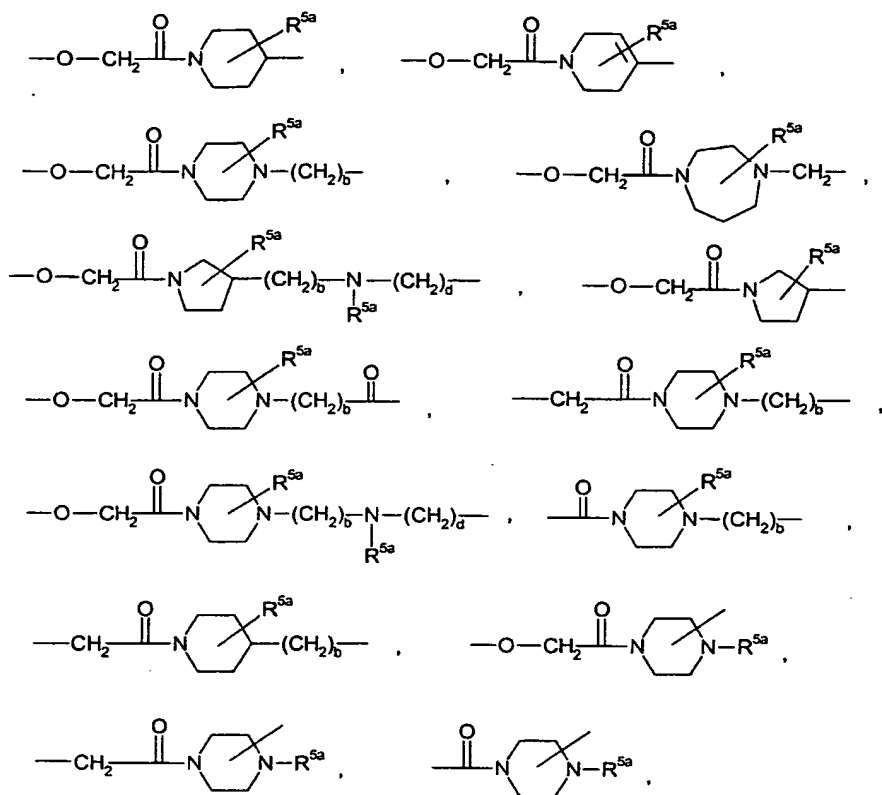


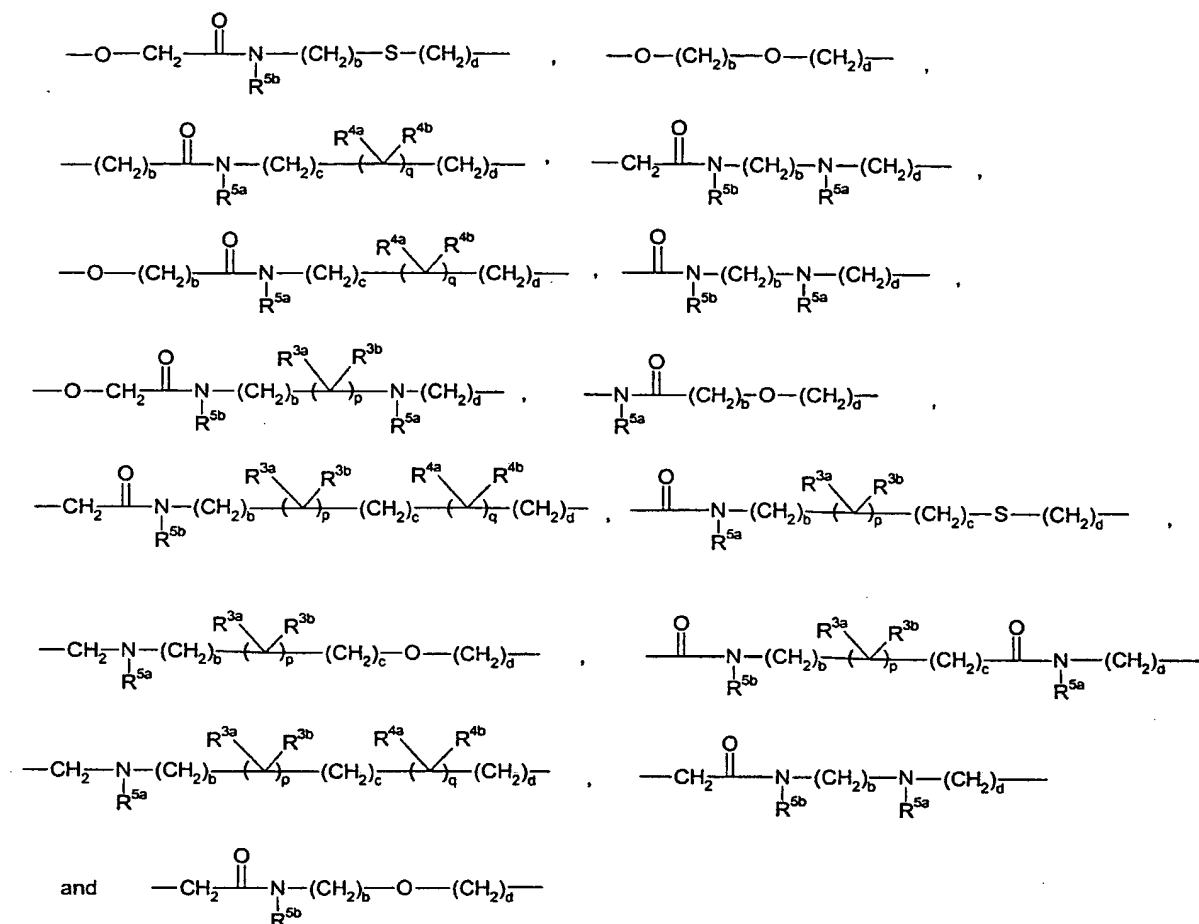


wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined for formula I.

- 5 In a further preferred embodiment K is selected from the group consisting of:







wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined for formula I.

- 5 In the above embodiments of K,  $R^{5a}$  and  $R^{5b}$  are preferably independently hydrogen, lower alkyl,  $-\text{OH}$ ,  $-(\text{CH}_2)_k\text{OR}^{6a}$ , aryl, aryl-lower alkyl,  $-\text{CH}_2\text{CF}_3$ ,  $-(\text{CH}_2)_g\text{-COOR}^{43}$ ,  $-\text{COOR}^{43}$ ,  $-(\text{CH}_2)_k\text{-CN}$  or  $-(\text{CH}_2)_k\text{-NR}^{6a}\text{R}^{6b}$  wherein  $g$ ,  $k$ ,  $R^{43}$ ,  $R^{6a}$  and  $R^{6b}$  are as defined for formula I.

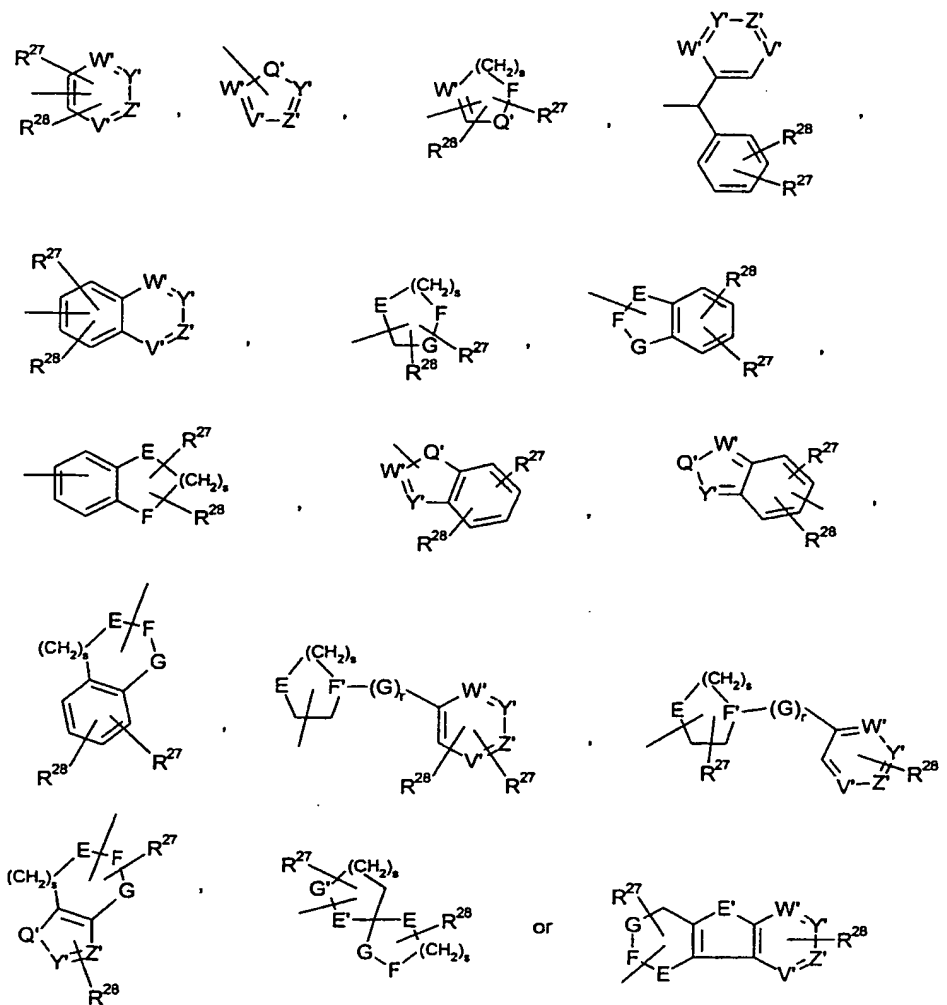
- 10 Preferably,  $g$  and  $k$  are independently 1, 2 or 3, and  $R^{6a}$  and  $R^{6b}$  are independently hydrogen, lower alkyl such as methyl or ethyl, or aryl such as phenyl,

In the above embodiments of K,  $R^{3a}$  and  $R^{3b}$  are preferably independently hydrogen, halogen,  $-\text{OH}$ ,  $-\text{O-lower alkyl}$ ,  $-\text{COO-lower alkyl}$ , lower alkyl or aryl-lower alkyl.

In the above embodiments of K,  $R^{4a}$  and  $R^{4b}$  are preferably independently hydrogen, -CN, -CONH<sub>2</sub>, -(CH<sub>2</sub>)-N(CH<sub>3</sub>)<sub>2</sub>, -O-lower alkyl, -CH<sub>2</sub>OH, -CH<sub>2</sub>O-aryl, -N(CH<sub>3</sub>)<sub>2</sub>, -OH, -CO<sub>2</sub>-lower alkyl or lower alkyl.

5

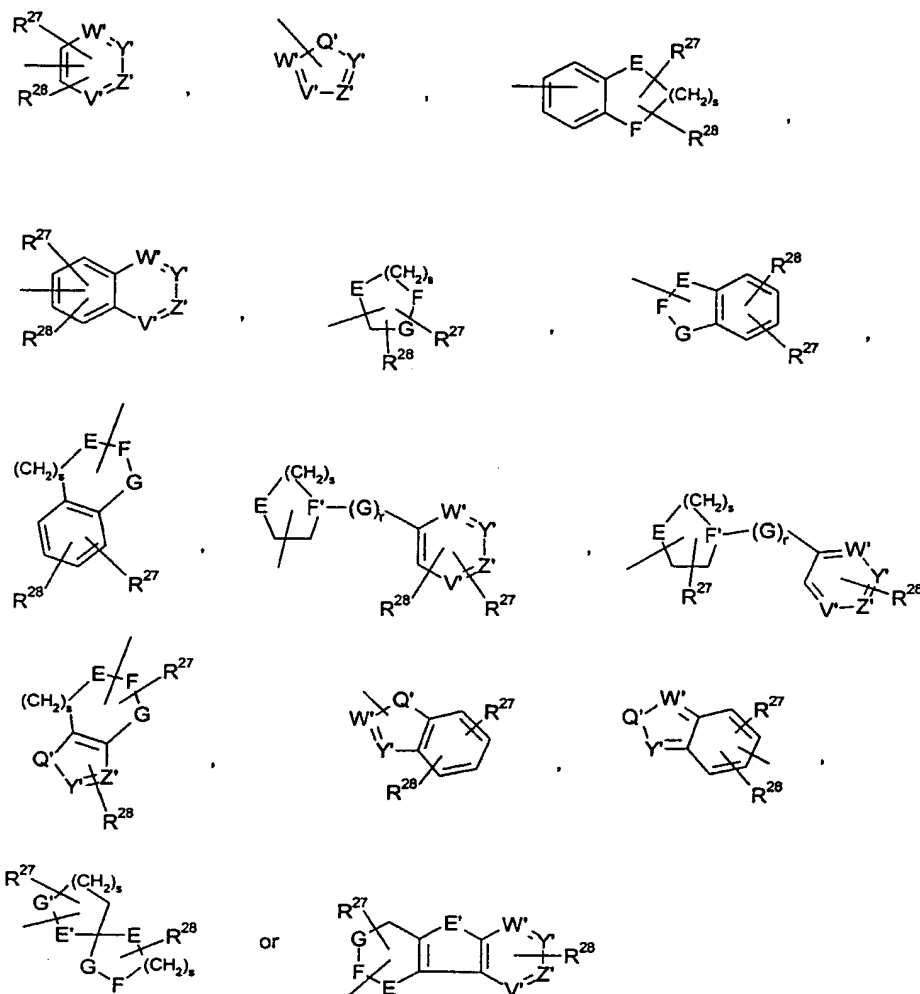
D is preferably hydrogen,



10 wherein s, r,  $R^{27}$ ,  $R^{28}$ , V', Y', Q', Z', W', E, E', F, F', G and G' are as defined for formula I.

In still a further preferred embodiment D is hydrogen,

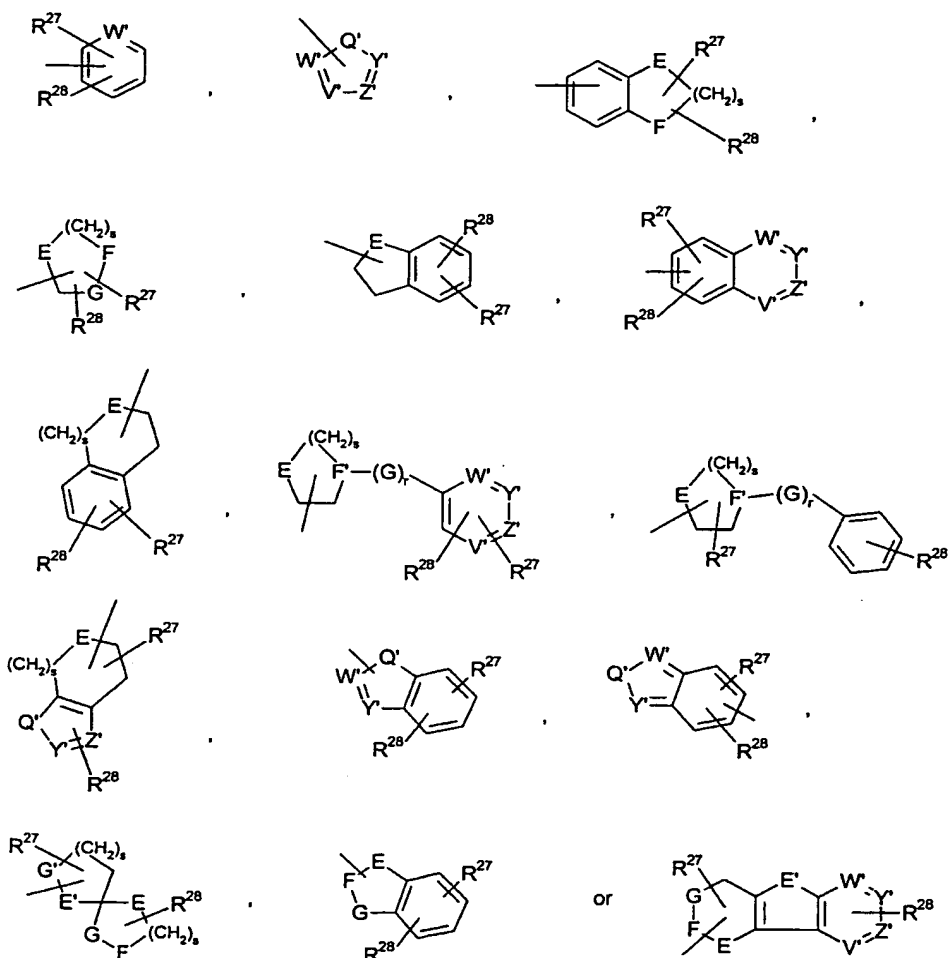
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wherein  $s$ ,  $r$ ,  $R^{27}$ ,  $R^{28}$ ,  $V'$ ,  $Y'$ ,  $Z'$ ,  $Q'$ ,  $Z'$ ,  $W'$ ,  $E$ ,  $E'$ ,  $F$ ,  $F'$ ,  $G$  and  $G'$  are as defined for formula I.

5

D is more preferably hydrogen,



- wherein E and E' independently are  $>CHR^{38}$ ,  $>NR^{39}$  or  $-O-$ ; F, G and G' independently are  $>CHR^{38}$ ,  $>C=O$  or  $>NR^{39}$ ; F' is  $>CR^{38}-$  or  $>N-$ ; and s, r,  $R^{27}$ ,  $R^{28}$ ,  $R^{38}$ ,  $R^{39}$ ,  $V'$ ,  $Y'$ ,  $Z'$ ,  $Q'$  and  $W'$  are as defined for formula I.

- $R^{27}$  and  $R^{28}$  are preferably independently hydrogen; halogen such as  $-Cl$ ,  $-Br$  or  $-F$ ;  $-CF_3$ ;  $-OCF_3$ ;  $-OCHF_2$ ;  $-OCH_2CF_3$ ;  $-(CH_2)_yNHCOCF_3$ ;  $-NHCOCF_3$ ;  $-CN$ ;  $-NO_2$ ;  $-COR^{29}$ ;  $-COOR^{29}$ ;  $-(CH_2)_yOR^{29}$  or  $-OR^{29}$  wherein  $R^{29}$  is hydrogen, aryl or lower alkyl and y is 1, 2, 3 or 4; lower alkyl such as methyl, ethyl, 2-propenyl, isopropyl, tert-butyl or cyclohexyl; lower alkylthio;  $-SCF_3$ ; aryl such as phenyl;  $-(CH_2)_yNR^{29}R^{30}$  or  $-NR^{29}R^{30}$  wherein  $R^{29}$  and  $R^{30}$  independently are hydrogen,  $-COO$ -lower alkyl or lower alkyl and y is 1, 2, 3 or 4; or  $-CONH_2$ ; or  $R^{27}$  and  $R^{28}$  together form a bridge  $-OCH_2O-$ ;  $R^{38}$  is hydrogen;  $-OCHF_2$ ;  $-OR^{40}$  wherein  $R^{40}$  is hydrogen or

lower alkyl; lower alkyl such as methyl, isopropyl or tert-butyl; lower alkylthio;  $-\text{SCF}_3$ ;  $-\text{CH}_2\text{OH}$ ;  $-\text{COO}$ -lower alkyl or  $-\text{CONH}_2$ ; and  $\text{R}^{39}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl.

In a further embodiment the invention relates to the compounds of the formula I wherein:

R<sup>1</sup> and R<sup>2</sup> independently are hydrogen or lower alkyl or together form a valence bond;

5 R<sup>3</sup> and R<sup>4</sup> independently are hydrogen or lower alkyl;

X is >C=O, >C=S, >C=NR<sup>5</sup> or >SO<sub>2</sub>;

n is 0, 1, 2 or 3;

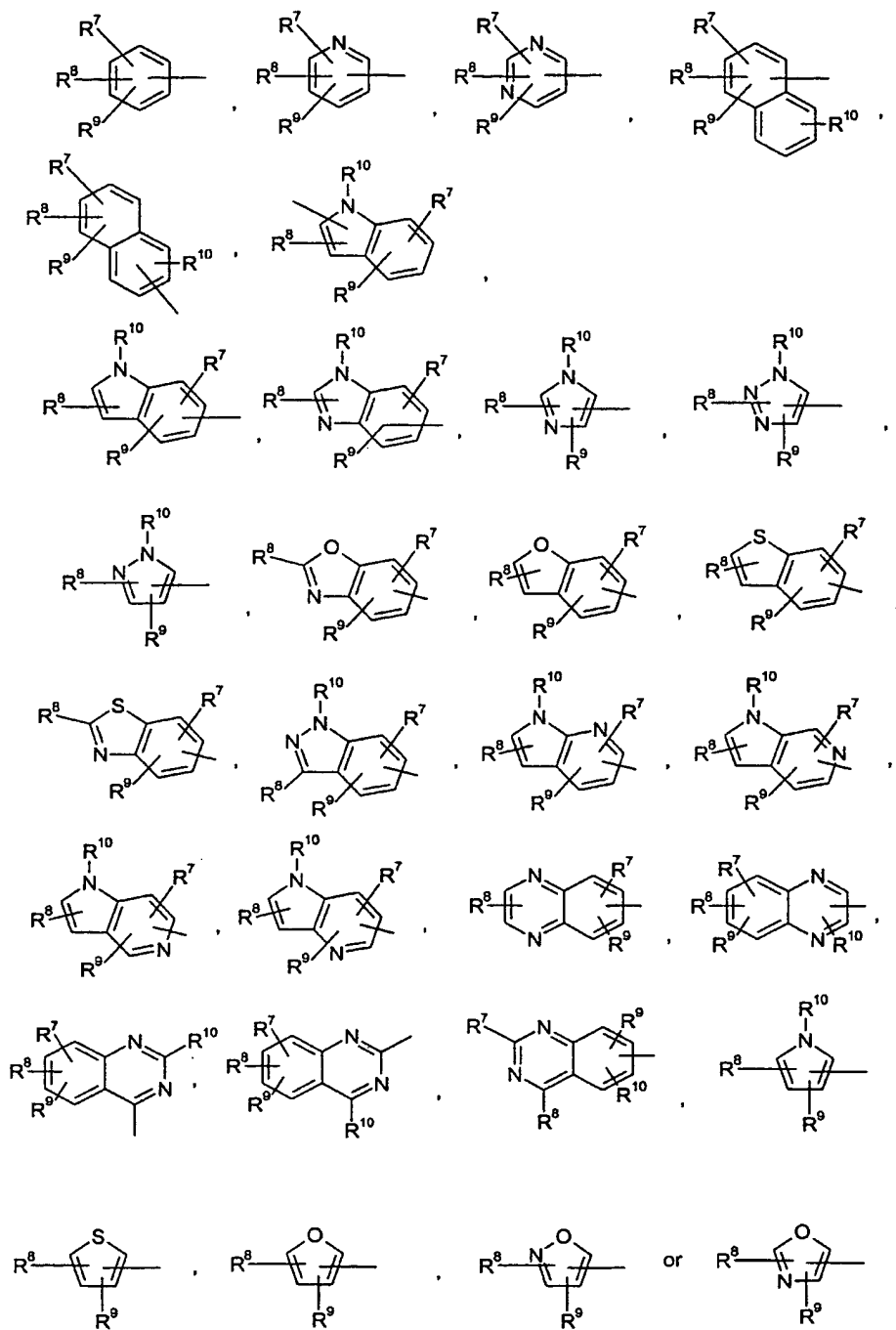
10

m is 0 or 1;

R<sup>5</sup> is hydrogen, lower alkyl, aryl-lower alkyl, or -OR<sup>6</sup>;

15 wherein R<sup>6</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

A is



wherein

$R^7$  is hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, -SCF<sub>3</sub>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup>, -OSO<sub>2</sub>CF<sub>3</sub>;

- 5  $R^8$  and  $R^9$  independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, -SCF<sub>3</sub>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup>, -OSO<sub>2</sub>CF<sub>3</sub>, or  $R^8$  and  $R^9$  together form a bridge -OCH<sub>2</sub>O-;

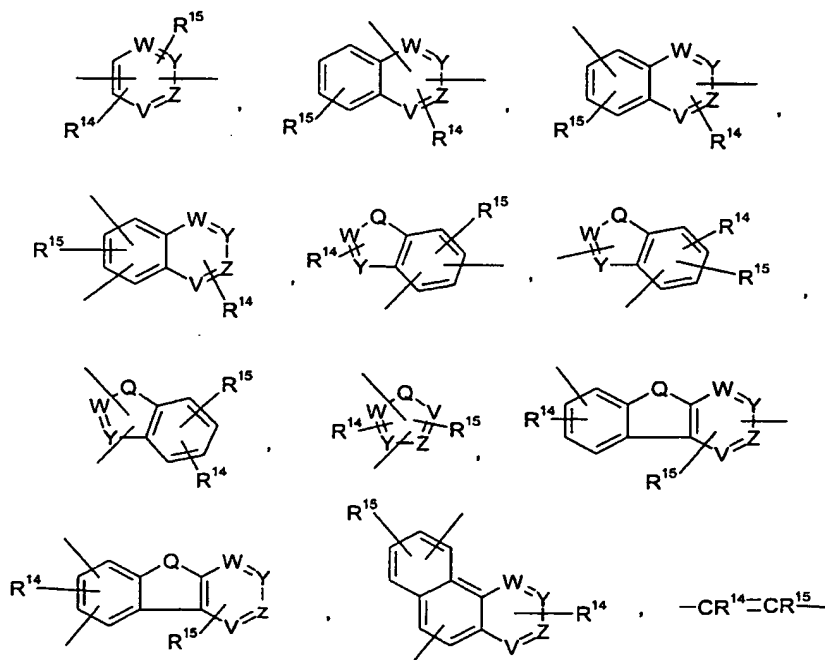
- 10  $R^{11}$  and  $R^{12}$  independently are hydrogen, -COR<sup>13</sup>, -SO<sub>2</sub>R<sup>13</sup>, lower alkyl or aryl;

$R^{13}$  is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

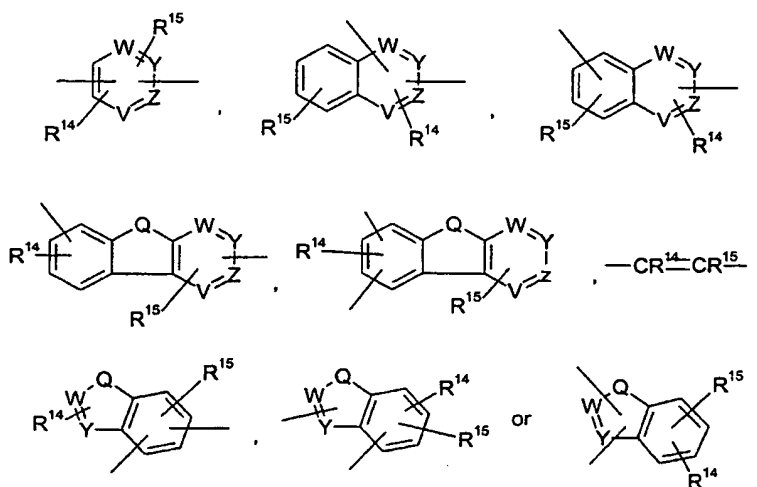
$R^{10}$  is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

15

B is



or a valence bond; preferably



- $R^{14}$  and  $R^{15}$  independently are hydrogen, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-O(CH_2)_lCF_3$ ,  $-NO_2$ ,  $-OR^{16}$ ,  $-NR^{16}R^{17}$ , lower alkyl, aryl,  $-SCF_3$ ,  $-SR^{16}$ ,  $-CHF_2$ ,  $-OCHF_2$ ,  $-OCF_2CHF_2$ ,  $-OSO_2CF_3$ ,  $-CONR^{16}R^{17}$ ,  $-(CH_2)_lCONR^{16}R^{17}$ ,  $-O(CH_2)_lCONR^{16}R^{17}$ ,  $-(CH_2)_lCOR^{16}$ ,  $-O(CH_2)_lCOR^{16}$ ,  $-(CH_2)_lOR^{16}$ ,  $-O(CH_2)_lOR^{16}$ ,  $-(CH_2)_lNR^{16}R^{17}$ ,  $-O(CH_2)_lNR^{16}R^{17}$ ,  $-OCOR^{16}$ ,  $-CO_2R^{18}$ ,  $-O(CH_2)_lCN$ ,  $-O(CH_2)_lCl$ , or  $R^{14}$  and  $R^{15}$  together form a bridge  $-O-CH_2-O-$ ;

- $R^{14}$  and  $R^{15}$  preferably independently representing hydrogen, halogen,  $-CF_3$ ,  $-OCF_3$ ,  $-OR^{16}$ ,  $-NR^{16}R^{17}$ , lower alkyl, aryl, aryl-lower alkyl,  $-OSO_2CF_3$ ,  $-CONR^{16}R^{17}$ ,  $-CH_2OR^{16}$ ,  $-CH_2NR^{16}R^{17}$ ,  $-OCOR^{16}$  or  $-CO_2R^{18}$ ; or together forming a bridge  $-OCH_2O-$ ;

$l$  is 1, 2, 3 or 4;

- $R^{16}$  and  $R^{17}$  independently are hydrogen,  $-COR^{18}$ ,  $-SO_2R^{18}$ , lower alkyl, aryl, or  $R^{16}$  and  $R^{17}$  together form a cyclic alkyl bridge containing from 2 to 7 carbon atoms;

$R^{18}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

- $W$  is  $-N=$  or  $-CR^{19}=$ ;

$Y$  is  $-N=$  or  $-CR^{20}=$ ;

Z is -N= or -CR<sup>21</sup>=;

V is -N= or -CR<sup>22</sup>=;

5 Q is -NR<sup>23</sup>-, -O- or -S-;

wherein:

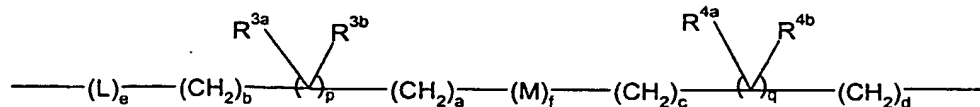
10 R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>24</sup>, -NR<sup>24</sup>R<sup>25</sup>, lower alkyl, aryl, aryl-lower alkyl, SCF<sub>3</sub>, -SR<sup>24</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -OCH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>OR<sup>24</sup>, -CH<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, -OCOR<sup>24</sup> or -CO<sub>2</sub>R<sup>24</sup>, or R<sup>19</sup> and R<sup>20</sup>, R<sup>20</sup> and R<sup>21</sup> or R<sup>21</sup> and R<sup>22</sup> together form a bridge -OCH<sub>2</sub>O-;

15 R<sup>24</sup> and R<sup>25</sup> independently are hydrogen, -COR<sup>26</sup>, -SO<sub>2</sub>R<sup>26</sup>, lower alkyl, aryl or aryl-lower alkyl;

R<sup>26</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

20 R<sup>23</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



25 wherein:

R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup> and R<sup>4b</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>24a</sup>, -NR<sup>24a</sup>R<sup>25a</sup>, lower alkyl, aryl, aryl-lower alkyl, SCF<sub>3</sub>, -SR<sup>24a</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>24a</sup>R<sup>25a</sup>, -CH<sub>2</sub>CONR<sup>24a</sup>R<sup>25a</sup>, -OCH<sub>2</sub>CONR<sup>24a</sup>R<sup>25a</sup>, -CH<sub>2</sub>OR<sup>24a</sup>, -CH<sub>2</sub>NR<sup>24a</sup>R<sup>25a</sup>, -OCOR<sup>24a</sup> or -CO<sub>2</sub>R<sup>24a</sup>;

30

wherein  $R^{24a}$  and  $R^{25a}$  independently are hydrogen,  $-\text{COR}^{26a}$ ,  $-\text{SO}_2\text{R}^{26a}$ , lower alkyl, aryl or aryl-lower alkyl;

$R^{26a}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl; or

5

$R^{3a}$  and  $R^{3b}$ ,  $R^{4a}$  and  $R^{4b}$  or  $R^{3a}$  and  $R^{4b}$  together form a bridge  $-(\text{CH}_2)_i-$ , wherein

i is 1, 2, 3 or 4;

10 

a, b, c and d independently are 0, 1, 2, 3 or 4;

e, f, p and q independently are 0 or 1;

L and M independently are

15

$-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{NR}^{5a}-$ ,  $-\text{COO}-$ ,  $-\text{CONR}^{5a}-$ ,  $-\text{NR}^{5a}\text{CO}-$ ,  $-\text{SO}-$ ,  $-\text{SO}_2-$ ,  $-\text{OSO}_2-$ ,  
 $-\text{SO}_2-\text{NR}^{5a}-$ ,  $-\text{NR}^{5a}\text{SO}_2-$ ,  $-\text{NR}^{5a}\text{CONR}^{5b}-$ ,  $-\text{NR}^{5a}\text{CSNR}^{5b}-$ ,  $-\text{OCONR}^{5b}-$  or  $-\text{NR}^{5a}\text{C}(\text{O})\text{O}-$

wherein  $R^{5a}$  and  $R^{5b}$  independently are hydrogen, lower alkyl,  $-(\text{CH}_2)_k-\text{OH}$ ,  $-(\text{CH}_2)_k-$

20 

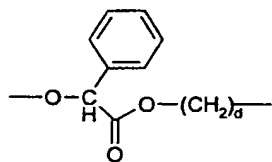
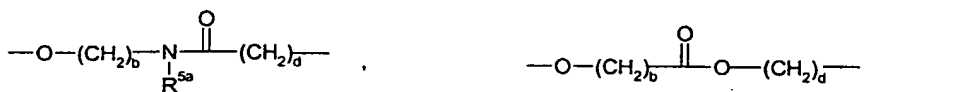
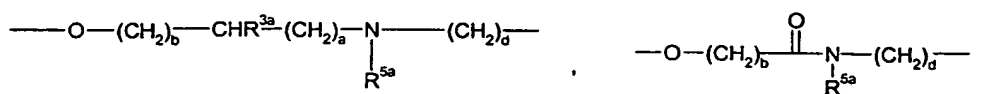
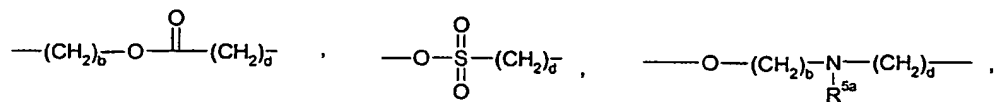
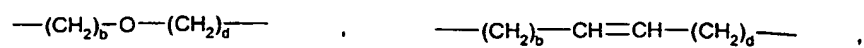
$\text{NR}^{6a}\text{R}^{6b}$ , aryl or aryl-lower alkyl;

wherein k is 2, 3 or 4;

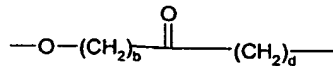
$R^{6a}$  and  $R^{6b}$  independently are hydrogen, lower alkyl or aryl-lower alkyl;

25

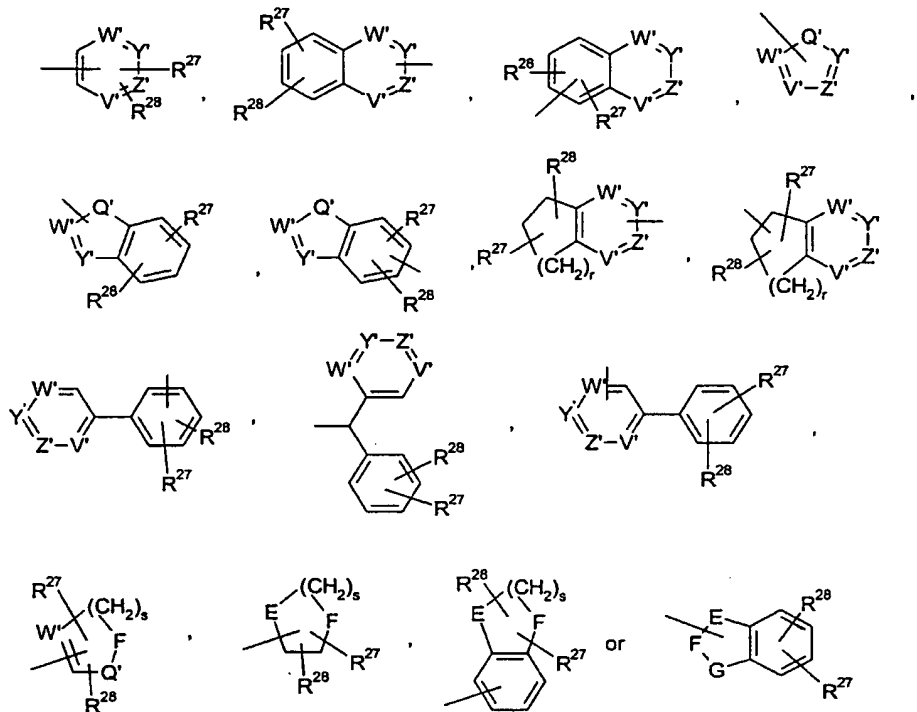
K preferably representing



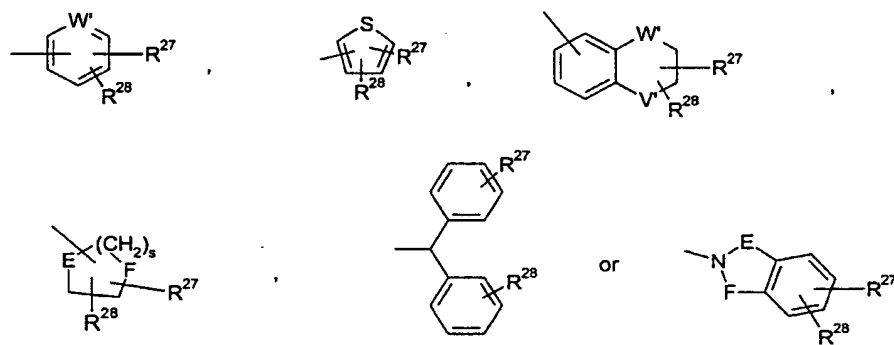
or



D is hydrogen or



preferably hydrogen,



5 wherein:

r and s independently are 1 or 2;

E, F and G independently are  $-\text{CHR}^{38}-$ ,  $>\text{C}=\text{O}$ ,  $>\text{NR}^{39}$ ,  $-\text{O}-$  or  $-\text{S}-$ ;

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Y' is  $-\text{N}=\text{}$  or  $-\text{CR}^{32}=\text{}$ ;

Z' is -N= or -CR<sup>33</sup>=;

V' is -N= or -CR<sup>34</sup>=;

5

W' is -N= or -CR<sup>35</sup>=;

Q' is -NR<sup>36</sup>-, -O- or -S-;

10 wherein

R<sup>27</sup>, R<sup>28</sup>, R<sup>32</sup>, R<sup>33</sup>, R<sup>34</sup> and R<sup>35</sup> are independently hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
 -O(CH<sub>2</sub>)<sub>y</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>29</sup>, -NR<sup>29</sup>R<sup>30</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>29</sup>,  
 -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>29</sup>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>29</sup>R<sup>30</sup>, -(CH<sub>2</sub>)<sub>y</sub>CONR<sup>29</sup>R<sup>30</sup>,  
 15 -O(CH<sub>2</sub>)<sub>y</sub>CONR<sup>29</sup>R<sup>30</sup>, -(CH<sub>2</sub>)<sub>y</sub>OR<sup>29</sup>, -(CH<sub>2</sub>)<sub>y</sub>NR<sup>29</sup>R<sup>30</sup>, -OCOR<sup>29</sup>, -CO<sub>2</sub>R<sup>29</sup>;  
 or R<sup>27</sup> and R<sup>28</sup>, R<sup>32</sup> and R<sup>33</sup>, R<sup>33</sup> and R<sup>34</sup> or R<sup>34</sup> and R<sup>35</sup> together form a bridge -OCH<sub>2</sub>O-;

R<sup>27</sup> and R<sup>28</sup> preferably independently representing hydrogen, halogen, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
 -OCH<sub>2</sub>CF<sub>3</sub>, -OR<sup>29</sup>, lower alkyl, aryl or aryl-lower alkyl, or together forming a bridge  
 20 -OCH<sub>2</sub>O-;

y is 1, 2, 3 or 4;

R<sup>29</sup> and R<sup>30</sup> independently are hydrogen, -COR<sup>31</sup>, -SO<sub>2</sub>R<sup>31</sup>, lower alkyl, aryl or aryl-lower  
 25 alkyl;

R<sup>31</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

R<sup>36</sup> and R<sup>39</sup> independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl;  
 30

R<sup>38</sup> is hydrogen, -OR<sup>40</sup>, -NR<sup>40</sup>R<sup>41</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>40</sup>, -CHF<sub>2</sub>, -  
 OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -CONR<sup>40</sup>R<sup>41</sup>, -(CH<sub>2</sub>)<sub>x</sub>CONR<sup>40</sup>R<sup>41</sup>, -O(CH<sub>2</sub>)<sub>x</sub>CONR<sup>40</sup>R<sup>41</sup>, -(CH<sub>2</sub>)<sub>x</sub>OR<sup>40</sup>,  
 -(CH<sub>2</sub>)<sub>x</sub>NR<sup>40</sup>R<sup>41</sup>, -OCOR<sup>40</sup> or -CO<sub>2</sub>R<sup>40</sup>;

x is 1, 2, 3 or 4;

5  $R^{40}$  and  $R^{41}$  independently are hydrogen,  $-COR^{42}$ ,  $-SO_2R^{42}$ , lower alkyl, aryl or aryl-lower alkyl; and

$R^{42}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl.

10 In a further embodiment the invention relates to the compounds of the formula I wherein:

$R^1$  and  $R^2$  independently are hydrogen or lower alkyl or together form a valence bond;

$R^3$  and  $R^4$  independently are hydrogen or lower alkyl;

15 n is 0, 1, 2 or 3;

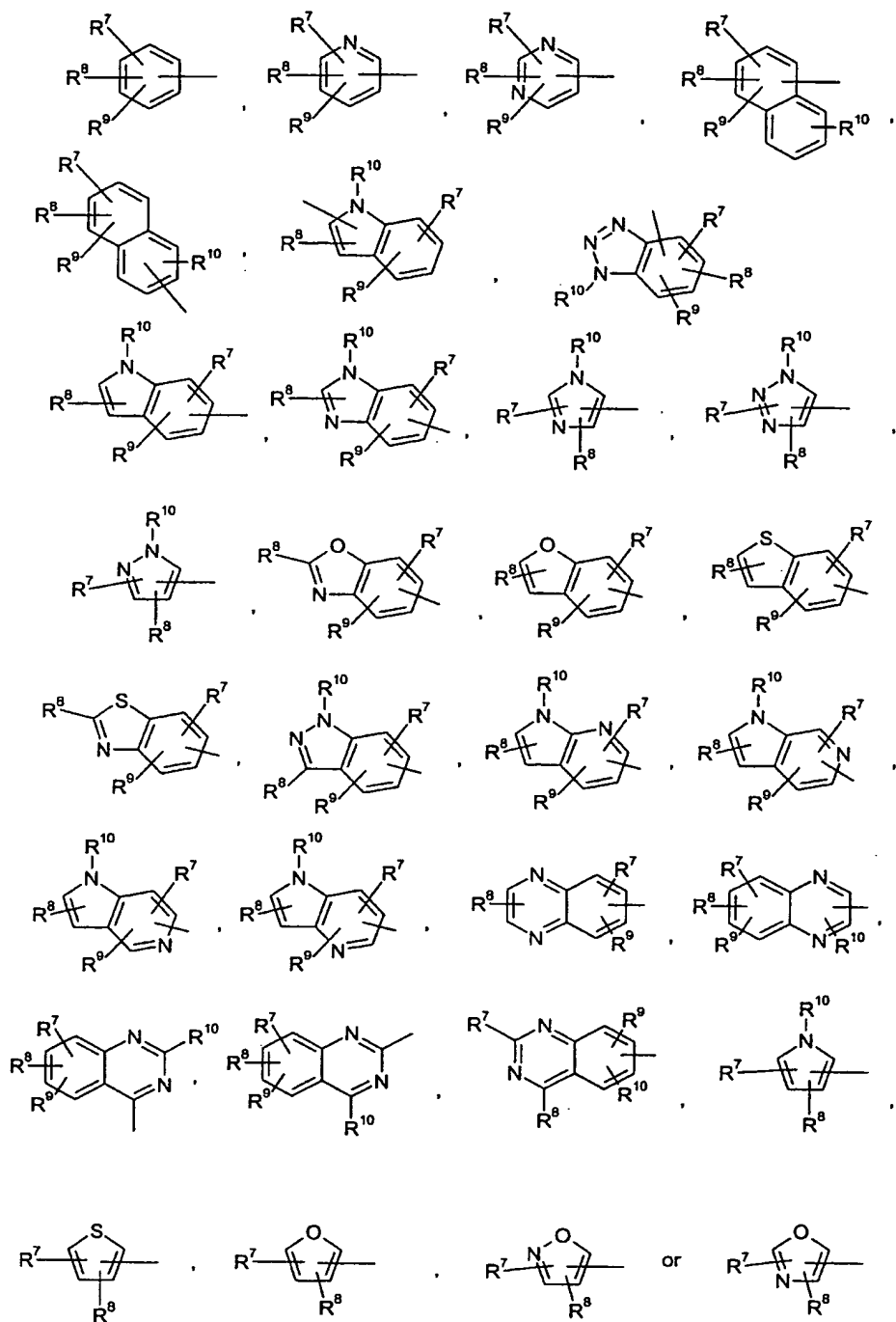
m is 0 or 1;

20 X is  $>C=O$ ,  $>C=S$ ,  $>C=NR^5$  or  $>SO_2$ ;

wherein  $R^5$  is hydrogen, lower alkyl, aryl-lower alkyl or  $-OR^6$ ;

wherein  $R^6$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

25 A is



R<sup>7</sup> is hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, -SCF<sub>3</sub>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup> or -OSO<sub>2</sub>CF<sub>3</sub>;

5

R<sup>8</sup> and R<sup>9</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, -SCF<sub>3</sub>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup> or -OSO<sub>2</sub>CF<sub>3</sub>, or R<sup>8</sup> and R<sup>9</sup> together form a bridge -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;

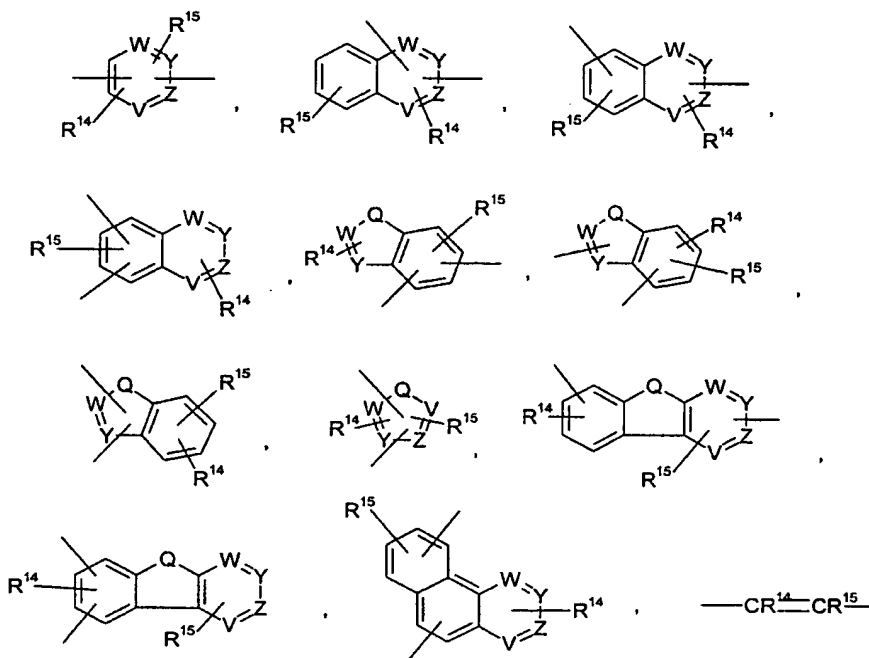
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wherein R<sup>11</sup> and R<sup>12</sup> independently are hydrogen, -COR<sup>13</sup>, -SO<sub>2</sub>R<sup>13</sup>, lower alkyl or aryl;

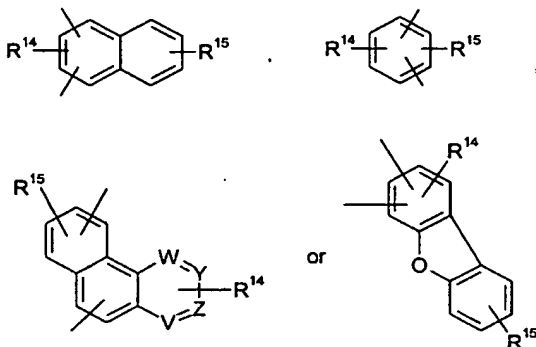
wherein R<sup>13</sup> is hydrogen, lower alkyl, aryl-lower alkyl or aryl; and

15 R<sup>10</sup> is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

B is



or a valence bond; preferably



wherein:

- 5 R<sup>14</sup> and R<sup>15</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -O(CH<sub>2</sub>)<sub>l</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>16</sup>, -NR<sup>16</sup>R<sup>17</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>16</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>16</sup>R<sup>17</sup>, -(CH<sub>2</sub>)<sub>l</sub>CONR<sup>16</sup>R<sup>17</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CONR<sup>16</sup>R<sup>17</sup>, -(CH<sub>2</sub>)<sub>l</sub>COR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>COR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>OR<sup>16</sup>, -O(CH<sub>2</sub>)<sub>l</sub>OR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>NR<sup>16</sup>R<sup>17</sup>, -O(CH<sub>2</sub>)<sub>l</sub>NR<sup>16</sup>R<sup>17</sup>, -OCOR<sup>16</sup>, -CO<sub>2</sub>R<sup>18</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CO<sub>2</sub>R<sup>18</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CN, -O(CH<sub>2</sub>)<sub>l</sub>Cl, or R<sup>14</sup> and R<sup>15</sup> together  
 10 form a bridge -OCH<sub>2</sub>O-;

R<sup>14</sup> and R<sup>15</sup> preferably independently representing hydrogen, halogen, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OR<sup>16</sup>, -NR<sup>16</sup>R<sup>17</sup>, lower alkyl, aryl, aryl-lower alkyl, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>16</sup>R<sup>17</sup>, -CH<sub>2</sub>OR<sup>16</sup>, -CH<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>, -OCOR<sup>16</sup> or -CO<sub>2</sub>R<sup>18</sup>; or together forming a bridge -OCH<sub>2</sub>O-;

15

wherein l is 1, 2, 3 or 4;

R<sup>16</sup> and R<sup>17</sup> independently are hydrogen, -COR<sup>18</sup>, -SO<sub>2</sub>R<sup>18</sup>, lower alkyl, aryl, or R<sup>16</sup> and R<sup>17</sup> together form a cyclic alkyl bridge containing from 2 to 7 carbon atoms;

20

wherein R<sup>18</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

W is -N= or -CR<sup>19</sup>=;

25 Y is -N= or -CR<sup>20</sup>=;

Z is -N= or -CR<sup>21</sup>=;

V is -N= or -CR<sup>22</sup>=; and

5 Q is -NR<sup>23</sup>-, -O- or -S-;

wherein:

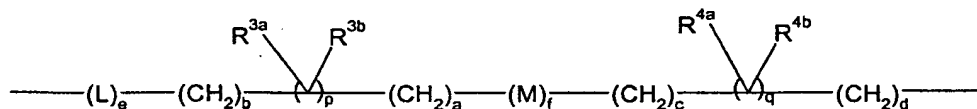
10 R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>24</sup>, -NR<sup>24</sup>R<sup>25</sup>, lower alkyl, aryl, aryl-lower alkyl, SCF<sub>3</sub>, -SR<sup>24</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -OCH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>OR<sup>24</sup>, -CH<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, -OCOR<sup>24</sup> or -CO<sub>2</sub>R<sup>24</sup>, or R<sup>19</sup> and R<sup>20</sup>, R<sup>20</sup> and R<sup>21</sup> or R<sup>21</sup> and R<sup>22</sup> together form a bridge -OCH<sub>2</sub>O-;

15 wherein R<sup>24</sup> and R<sup>25</sup> independently are hydrogen, -COR<sup>26</sup>, -SO<sub>2</sub>R<sup>26</sup>, lower alkyl, aryl or aryl-lower alkyl;

wherein R<sup>26</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

20 R<sup>23</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



25 wherein:

30 R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup> and R<sup>4b</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>24a</sup>, -NR<sup>24a</sup>R<sup>25a</sup>, lower alkyl, aryl, aryl-lower alkyl, SCF<sub>3</sub>, -SR<sup>24a</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>24a</sup>R<sup>25a</sup>, -CH<sub>2</sub>CONR<sup>24a</sup>R<sup>25a</sup>, -OCH<sub>2</sub>CONR<sup>24a</sup>R<sup>25a</sup>, -CH<sub>2</sub>OR<sup>24a</sup>, -CH<sub>2</sub>NR<sup>24a</sup>R<sup>25a</sup>, -OCOR<sup>24a</sup> or -CO<sub>2</sub>R<sup>24a</sup>;

wherein  $R^{24a}$  and  $R^{25a}$  independently are hydrogen,  $-\text{COR}^{26a}$ ,  $-\text{SO}_2\text{R}^{26a}$ , lower alkyl, aryl or aryl-lower alkyl;

wherein  $R^{26a}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

5

or

$R^{3a}$  and  $R^{3b}$ ,  $R^{4a}$  and  $R^{4b}$  or  $R^{3a}$  and  $R^{4b}$  together form a bridge  $-(\text{CH}_2)_i$ ;

10 wherein  $i$  is 1, 2, 3 or 4;

$a$ ,  $b$ ,  $c$  and  $d$  independently are 0, 1, 2, 3 or 4;

$e$ ,  $f$  and  $p$  independently are 0 or 1;

15

$q$  is 0, 1 or 2; and

$L$  and  $M$  independently are

20  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{NR}^{5a}-$ ,  $-\text{CO}-$ ,  $-\text{OCO}-$ ,  $-\text{COO}-$ ,  $-\text{CONR}^{5a}-$ ,  $-\text{NR}^{5a}\text{CO}-$ ,  $-\text{SO}-$ ,  
 $-\text{SO}_2-$ ,  $-\text{OSO}_2-$ ,  $-\text{SO}_2-\text{NR}^{5a}-$ ,  $-\text{NR}^{5a}\text{SO}_2-$ ,  $-\text{NR}^{5a}\text{CONR}^{5b}-$ ,  $-\text{NR}^{5a}\text{CSNR}^{5b}-$ ,  $-\text{OCONR}^{5b}-$  or  
 $-\text{NR}^{5a}\text{C}(\text{O})\text{O}-$ ;

wherein  $R^{5a}$  and  $R^{5b}$  independently are hydrogen, lower alkyl,  $-(\text{CH}_2)_k-\text{OH}$ ,  $-(\text{CH}_2)_k-$

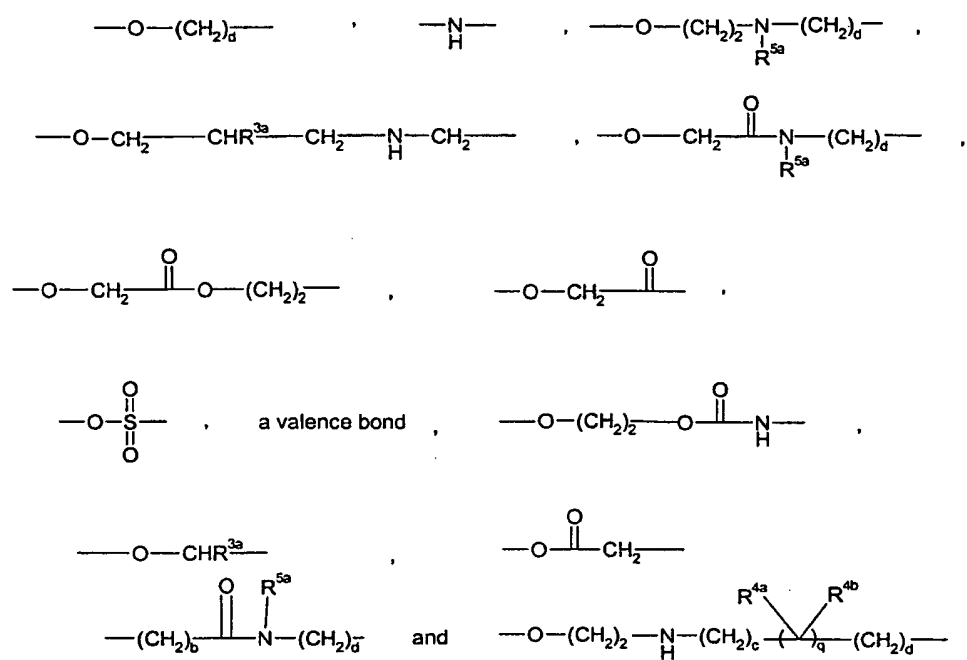
25  $\text{NR}^{6a}\text{R}^{6b}$ , aryl or aryl-lower alkyl;

wherein  $k$  is 2, 3 or 4; and

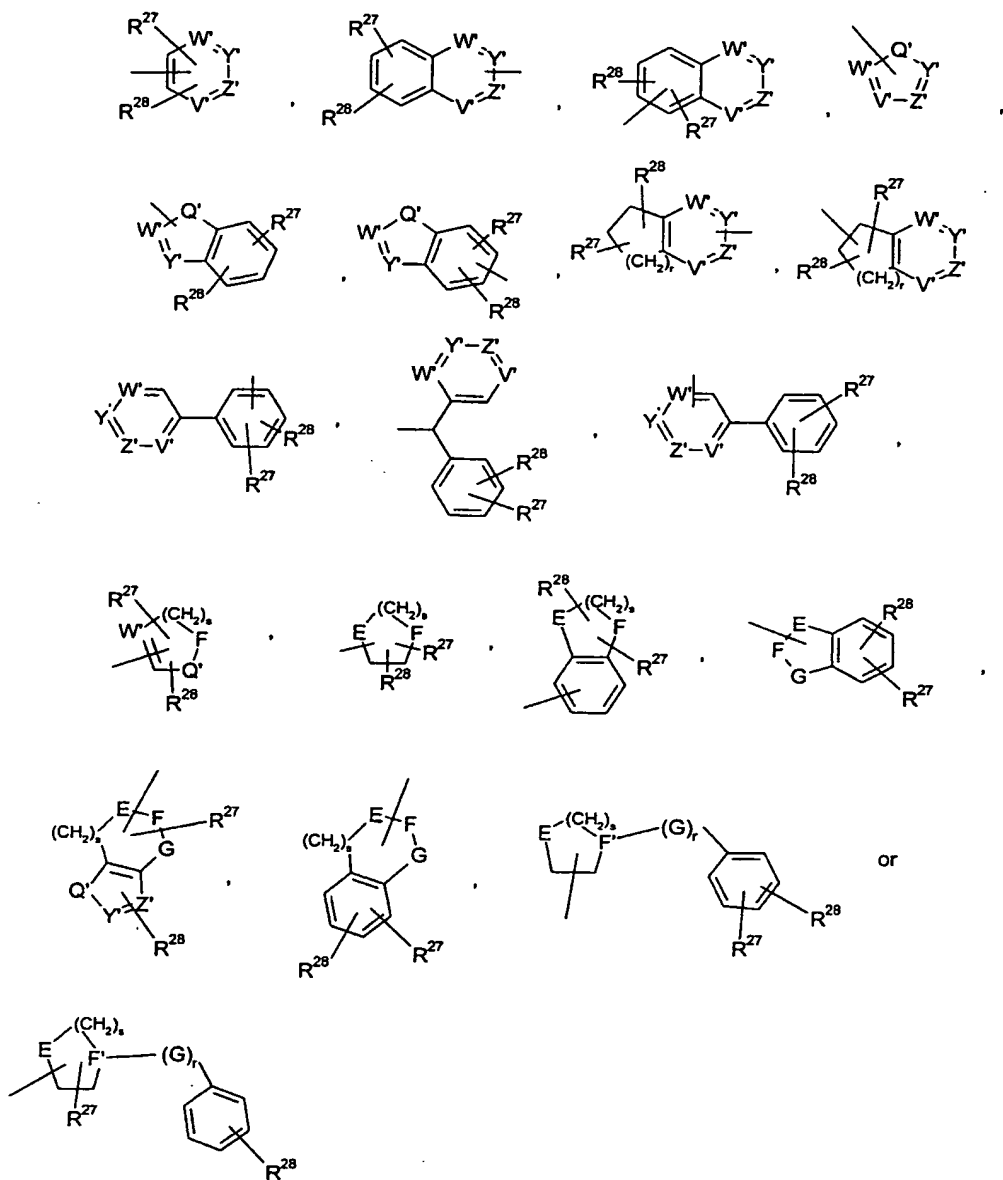
$R^{6a}$  and  $R^{6b}$  independently are hydrogen, lower alkyl or aryl-lower alkyl;

30

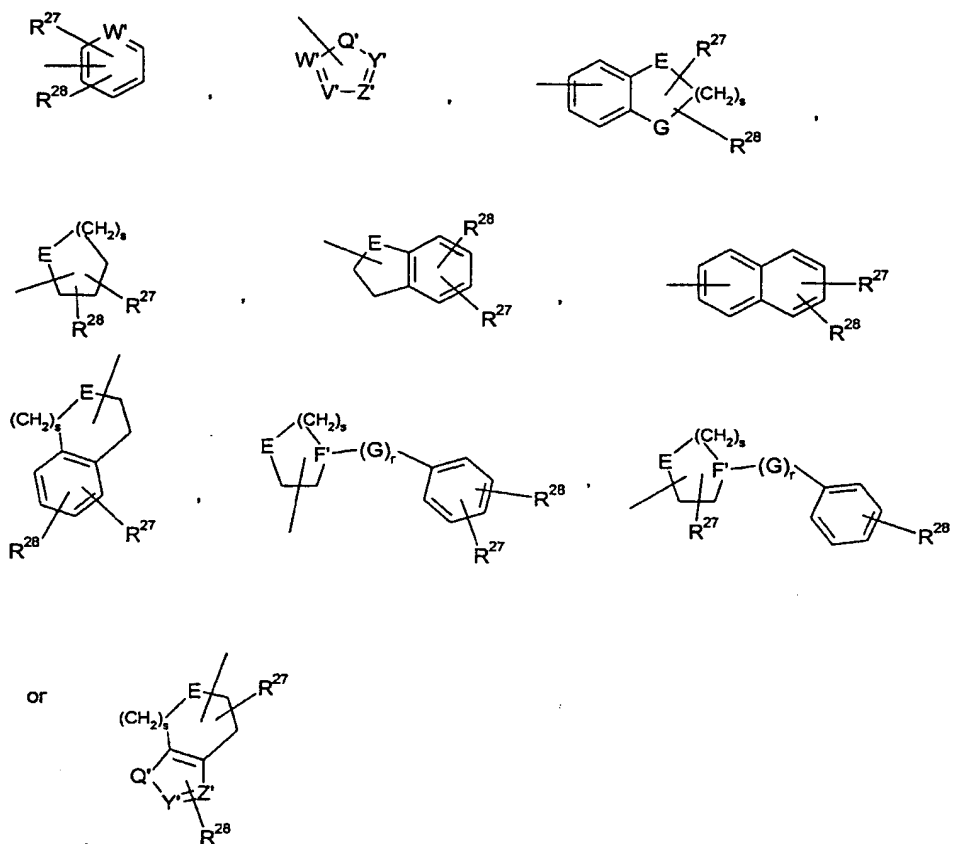
$K$  preferably representing



D is hydrogen,



preferably hydrogen,



wherein:

5

$r$  and  $s$  independently are 0, 1 or 2;

E, F and G independently are -CHR<sup>38</sup>-, >C=O, >NR<sup>39</sup>-, -O- or -S-;

10 F' is  $>CR^{38}$ - or  $>N$ -;

Y' is -N= or -CR<sup>32</sup>=;

Z' is -N= or -CR<sup>33</sup>=;

15

V' is -N= or -CR<sup>34</sup>=;

W' is -N= or -CR<sup>35</sup>=; and

Q' is -NR<sup>36</sup>-, -O- or -S-;

5 wherein:

R<sup>27</sup>, R<sup>28</sup>, R<sup>32</sup>, R<sup>33</sup>, R<sup>34</sup> and R<sup>35</sup> are independently hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
 -O(CH<sub>2</sub>)<sub>y</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>29</sup>, -NR<sup>29</sup>R<sup>30</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>29</sup>,  
 -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>29</sup>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>29</sup>R<sup>30</sup>, -(CH<sub>2</sub>)<sub>y</sub>CONR<sup>29</sup>R<sup>30</sup>,  
 10 -O(CH<sub>2</sub>)<sub>y</sub>CONR<sup>29</sup>R<sup>30</sup>, -(CH<sub>2</sub>)<sub>y</sub>OR<sup>29</sup>, -(CH<sub>2</sub>)<sub>y</sub>NR<sup>29</sup>R<sup>30</sup>, -OCOR<sup>29</sup> or -CO<sub>2</sub>R<sup>29</sup>;

or

R<sup>27</sup> and R<sup>28</sup>, R<sup>32</sup> and R<sup>33</sup>, R<sup>33</sup> and R<sup>34</sup> or R<sup>34</sup> and R<sup>35</sup> together form a bridge -OCH<sub>2</sub>O-;

15

R<sup>27</sup> and R<sup>28</sup> preferably independently representing hydrogen; halogen such as -Cl or -F;  
 -CF<sub>3</sub>; -OCF<sub>3</sub>; -OCHF<sub>2</sub>; -OCH<sub>2</sub>CF<sub>3</sub>; -OR<sup>29</sup> wherein R<sup>29</sup> is hydrogen or lower alkyl; lower  
 alkyl such as methyl, isopropyl or tert-butyl; lower alkylthio; -SCF<sub>3</sub>; -CH<sub>2</sub>OH; -COO-lower  
 alkyl; aryl or -CONH<sub>2</sub>; or together forming a bridge -OCH<sub>2</sub>O-;

20

wherein y is 1, 2, 3 or 4; and

R<sup>29</sup> and R<sup>30</sup> independently are hydrogen, -COR<sup>31</sup>, -SO<sub>2</sub>R<sup>31</sup>, lower alkyl, aryl or aryl-lower  
 alkyl;

25

wherein R<sup>31</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

R<sup>36</sup> and R<sup>39</sup> independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

30 R<sup>38</sup> is hydrogen, -OR<sup>40</sup>, -NR<sup>40</sup>R<sup>41</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>40</sup>, -CHF<sub>2</sub>,  
 -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -CONR<sup>40</sup>R<sup>41</sup>, -(CH<sub>2</sub>)<sub>x</sub>CONR<sup>40</sup>R<sup>41</sup>, -O(CH<sub>2</sub>)<sub>x</sub>CONR<sup>40</sup>R<sup>41</sup>, -(CH<sub>2</sub>)<sub>x</sub>OR<sup>40</sup>,  
 -(CH<sub>2</sub>)<sub>x</sub>NR<sup>40</sup>R<sup>41</sup>, -OCOR<sup>40</sup> or -CO<sub>2</sub>R<sup>40</sup>;

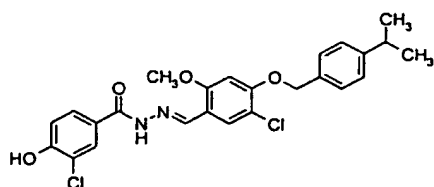
wherein x is 1, 2, 3 or 4;

R<sup>40</sup> and R<sup>41</sup> independently are hydrogen, -COR<sup>42</sup>, -SO<sub>2</sub>R<sup>42</sup>, lower alkyl, aryl or aryl-lower alkyl; and

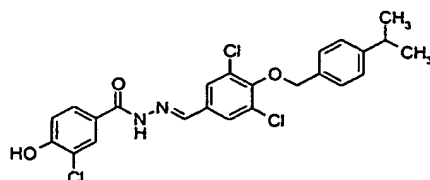
5

wherein R<sup>42</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl.

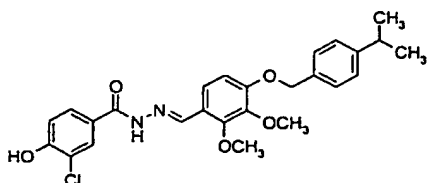
Examples of specific compounds represented by the above general formula V are the following:



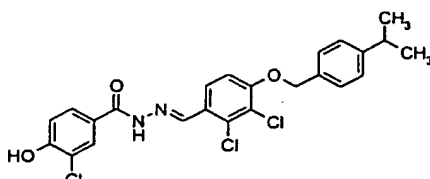
3-Chloro-4-hydroxybenzoic acid [5-chloro-2-methoxy-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



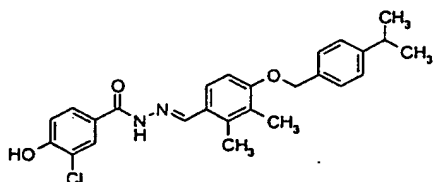
3-Chloro-4-hydroxybenzoic acid [3,5-dichloro-4-(4-isopropylbenzyloxy)benzylidene]hydrazide



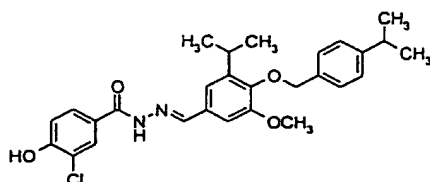
3-Chloro-4-hydroxybenzoic acid [2,3-dimethoxy-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



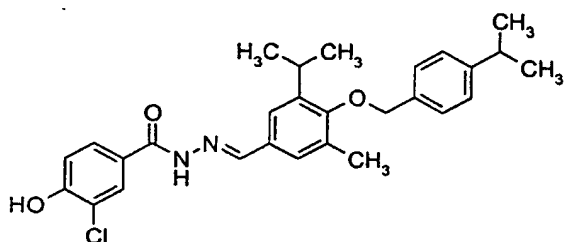
3-Chloro-4-hydroxybenzoic acid [2,3-dichloro-4-(4-isopropylbenzyloxy)benzylidene]hydrazide



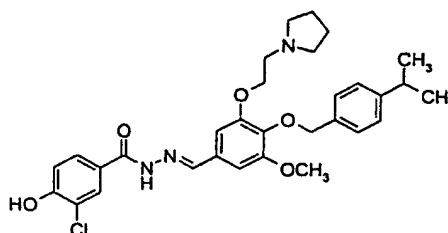
3-Chloro-4-hydroxybenzoic acid [2,3-dimethyl-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



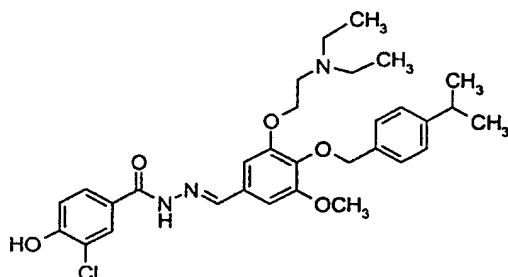
3-Chloro-4-hydroxybenzoic acid [3-isopropyl-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene]hydrazide



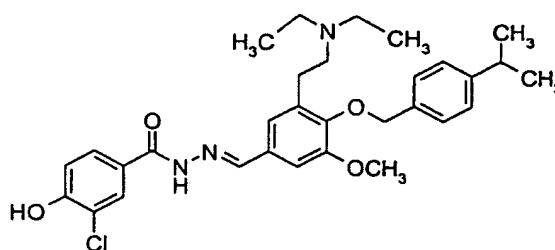
3-Chloro-4-hydroxybenzoic acid [3-isopropyl-4-(4-isopropylbenzyloxy)-5-methylbenzylidene]hydrazide



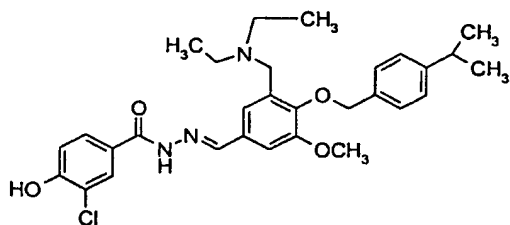
3-Chloro-4-hydroxybenzoic acid {3-[2-(1-pyrrolidino)ethoxy]}-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene}hydrazide



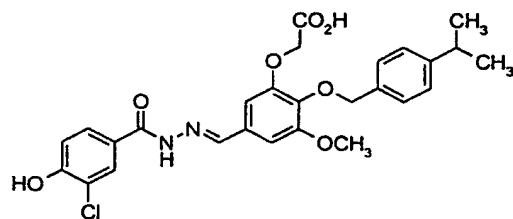
3-Chloro-4-hydroxybenzoic acid [3-(2-diethylaminoethoxy)-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene]hydrazide



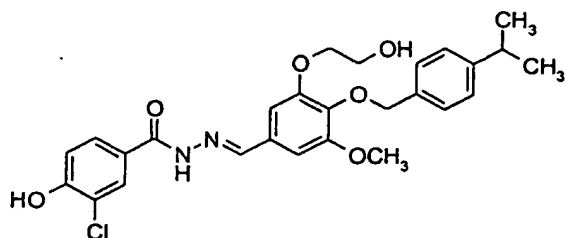
3-Chloro-4-hydroxybenzoic acid [3-(2-diethylaminoethyl)-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene]hydrazide



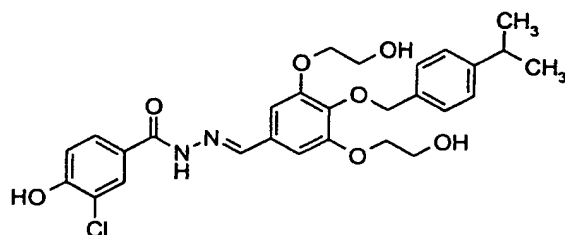
3-Chloro-4-hydroxybenzoic acid [3-diethylaminomethyl-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene]hydrazide



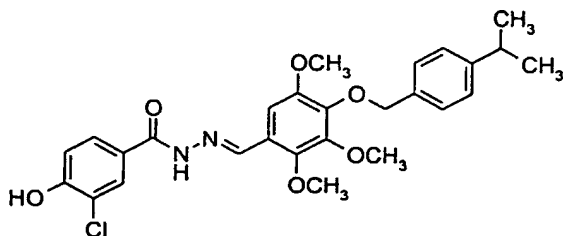
5-[(3-Chloro-4-hydroxybenzoyl)hydrazono-methyl]-3-methoxy-2-(4-isopropylbenzyloxy)-phenoxyacetic acid



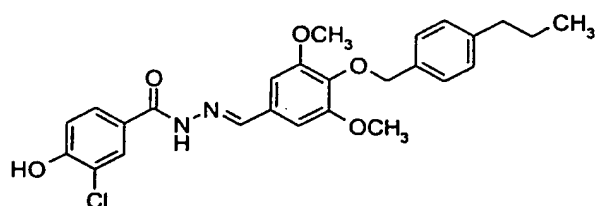
3-Chloro-4-hydroxybenzoic acid  
[3-(2-hydroxyethoxy)-4-(4-isopropyl-  
benzyloxy)-5-methoxybenzylidene]hydrazide



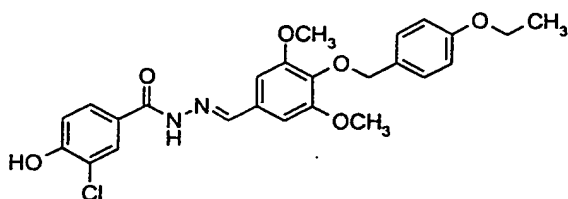
3-Chloro-4-hydroxybenzoic acid  
[3,5-bis-(2-hydroxyethoxy)-4-(4-  
isopropylbenzyloxy)benzylidene]hydrazide



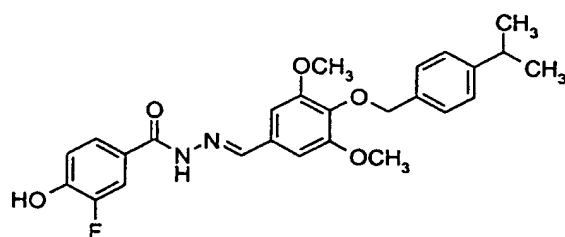
3-Chloro-4-hydroxybenzoic acid  
[2,3,5-trimethoxy-4-(4-isopropylbenzyloxy)-  
benzylidene]hydrazide



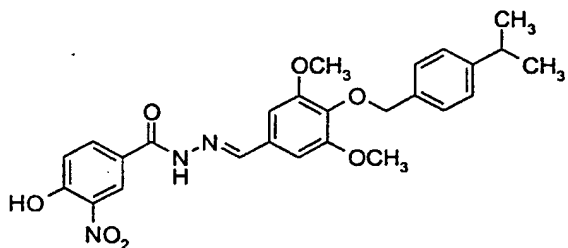
3-Chloro-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-n-propylbenzyloxy)-  
benzylidene]hydrazide



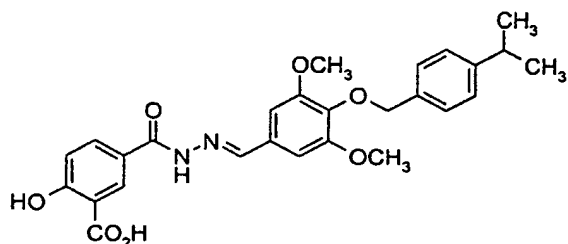
3-Chloro-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-ethoxybenzyloxy)-  
benzylidene]hydrazide



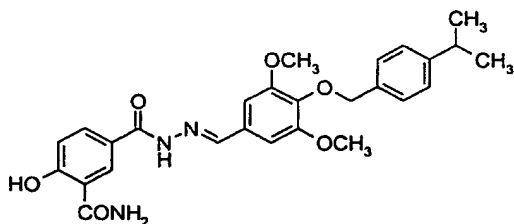
3-Fluoro-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-isopropylbenzyloxy)-  
benzylidene]hydrazide



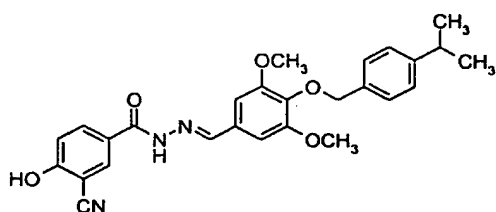
3-Nitro-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-isopropylbenzyloxy)-  
benzylidene]hydrazide



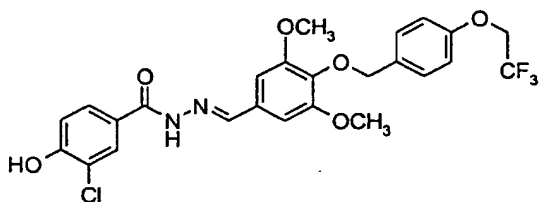
3-Carboxy-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-isopropylbenzyloxy)-ben-  
zylidene]hydrazide



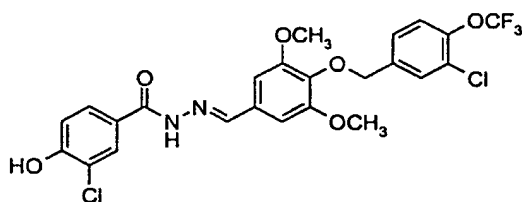
3-Carbamoyl-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-isopropylbenzyloxy)-  
benzylidene]hydrazide



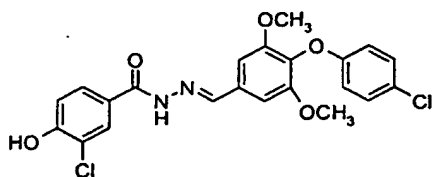
3-Cyano-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(4-isopropylbenzyloxy)-  
benzylidene]hydrazide



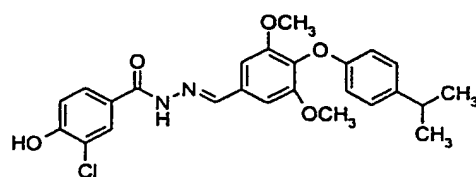
3-Chloro-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-[4-(2,2,2-trifluoroethoxy)-  
benzyloxy]-benzylidene]hydrazide



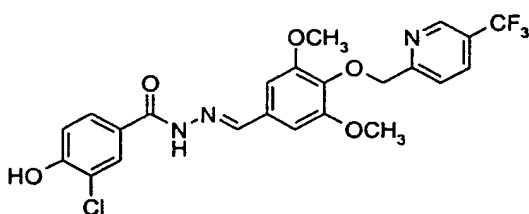
3-Chloro-4-hydroxybenzoic acid  
[3,5-dimethoxy-4-(3-chloro-4-  
trifluoromethoxybenzyloxy)benzylid-  
ene]hydrazide



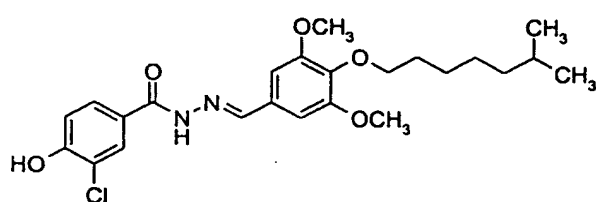
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-chlorophenoxy) benzylidene]hydrazide



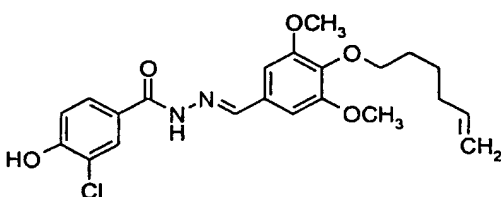
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-isopropylphenoxy) benzylidene]hydrazide



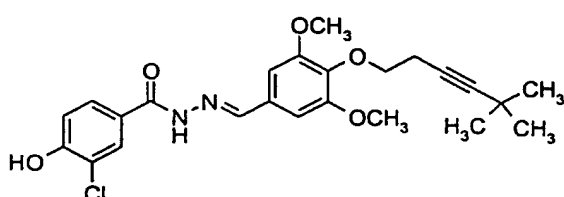
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-trifluoromethyl-2-pyridylmethoxy)- benzylidene]hydrazide



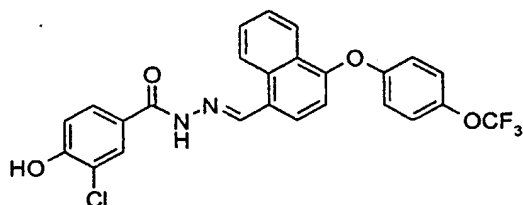
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(6-methylheptyloxy) benzylidene]hydrazide



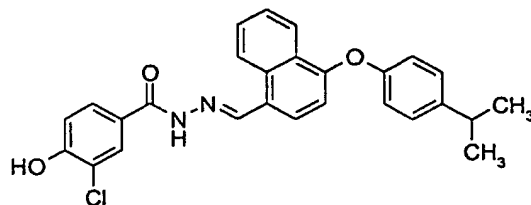
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(5-hexenyloxy) benzylidene]hydrazide



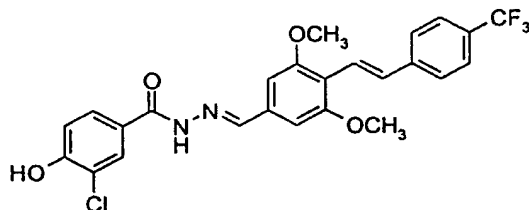
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(5,5-dimethyl-3-hexynyloxy) benzylidene]hydrazide



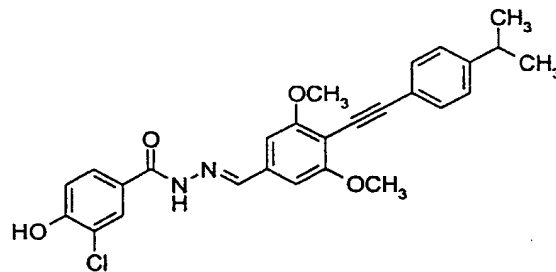
3-Chloro-4-hydroxybenzoic acid [4-(4-trifluoromethoxyphenoxy)-1-naphthylmethylene]hydrazide



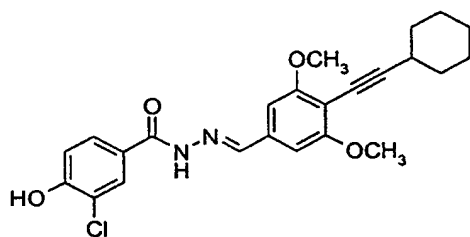
3-Chloro-4-hydroxybenzoic acid [4-(4-isopropylphenoxy)-1-naphthylmethylene]hydrazide



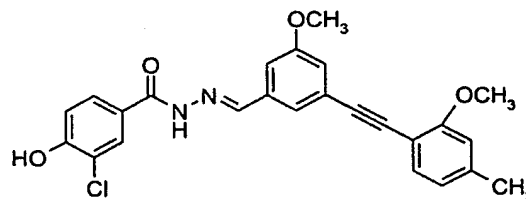
3-Chloro-4-hydroxybenzoic acid {3,5-dimethoxy-4-[2-(4-E-trifluoromethylphenyl)-ethenyl]benzylidene}hydrazide



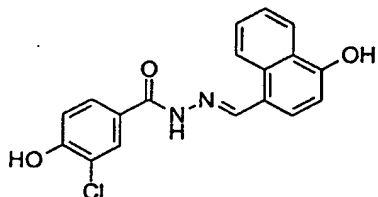
3-Chloro-4-hydroxybenzoic acid {3,5-dimethoxy-4-[(4-isopropylphenyl)-ethynyl]benzylidene}hydrazide



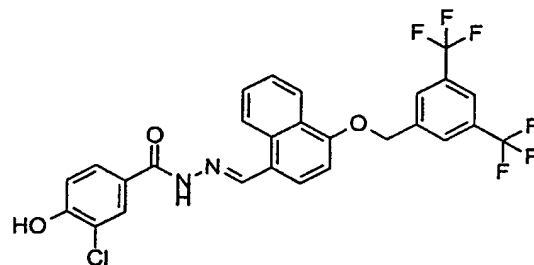
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(cyclohexylethynyl)benzylidene]hydrazide



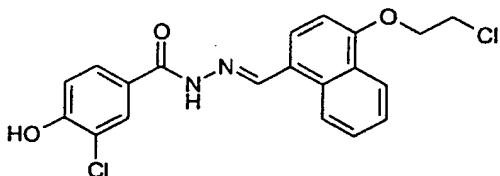
3-Chloro-4-hydroxybenzoic acid [3-(2-methoxy-4-methylphenyl)ethynyl-5-methoxybenzylidene]hydrazide



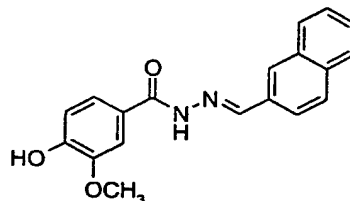
3-Chloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



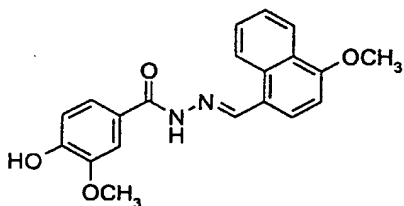
3-chloro-4-hydroxybenzoic acid [4-(3,5-bis-trifluoromethylbenzyloxy)-1-naphthylmethylene]hydrazide



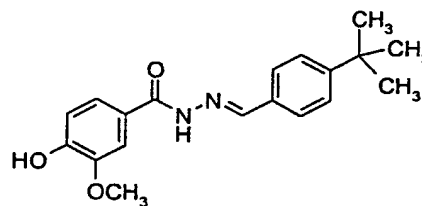
3-chloro-4-hydroxybenzoic acid [4-(2-chloroethoxy)-1-naphthylmethylene]hydrazide



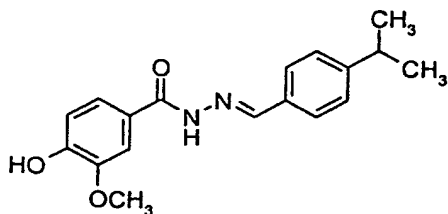
4-Hydroxy-3-methoxybenzoic acid (2-naphthylmethylene)hydrazide



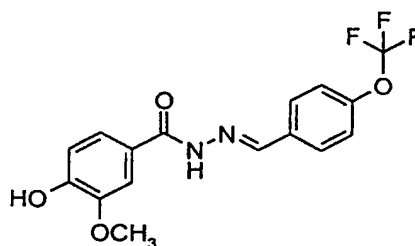
4-Hydroxy-3-methoxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide



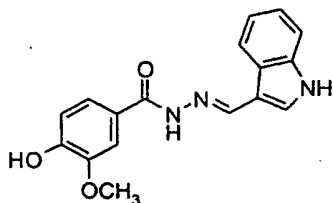
4-Hydroxy-3-methoxybenzoic acid (4-tert-butylbenzylidene)hydrazide



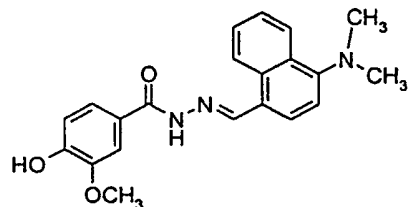
4-Hydroxy-3-methoxybenzoic acid (4-isopropylbenzylidene)hydrazide



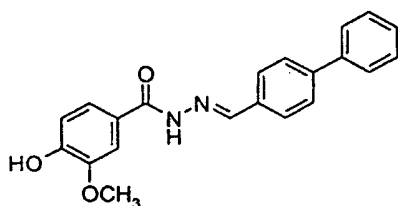
4-Hydroxy-3-methoxybenzoic acid (4-trifluoromethoxybenzylidene)hydrazide



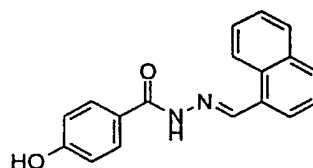
4-Hydroxy-3-methoxybenzoic acid (1H-indol-3-ylmethylene)hydrazide



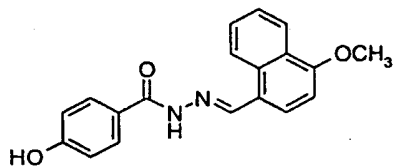
4-Hydroxy-3-methoxybenzoic acid (4-dimethylamino-1-naphthylmethylene)hydrazide



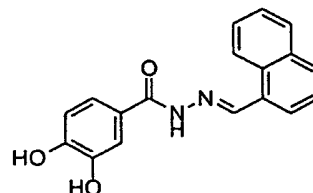
4-Hydroxy-3-methoxybenzoic acid (4-phenylbenzylidene)hydrazide



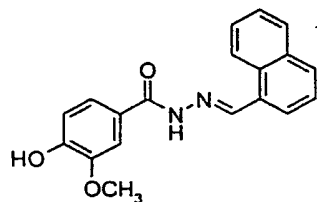
4-Hydroxybenzoic acid (1-naphthylmethylene)hydrazide



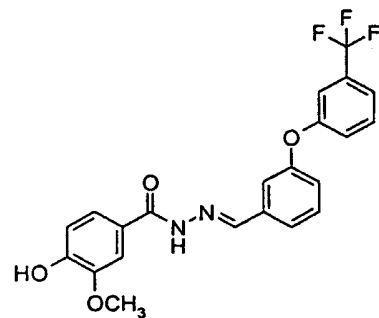
4-Hydroxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide



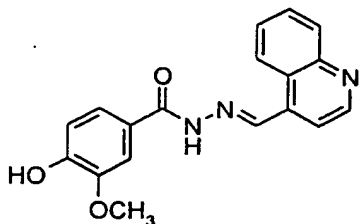
3,4-Dihydroxybenzoic acid (1-naphthylmethylene)hydrazide



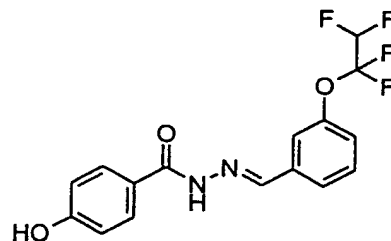
4-Hydroxy-3-methoxybenzoic acid (1-naphthylmethylene)hydrazide



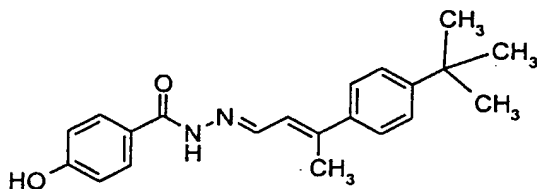
4-Hydroxy-3-methoxybenzoic acid [3-(3-trifluoromethylphenoxy)benzylidene]hydrazide



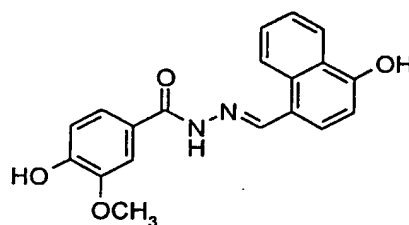
4-Hydroxy-3-methoxybenzoic acid (4-quinolinylmethylene)hydrazide



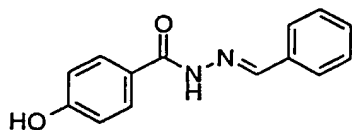
4-Hydroxybenzoic acid [3-(1,1,2,2-tetrafluoroethoxy)benzylidene]hydrazide



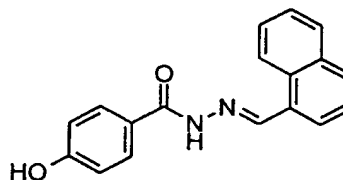
4-Hydroxybenzoic acid [3-(4-tert-butylphenyl)-E-but-2-enylidene]hydrazide



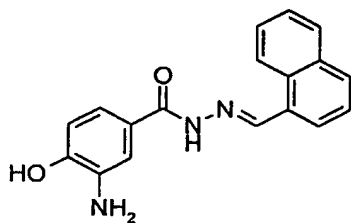
4-Hydroxy-3-methoxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



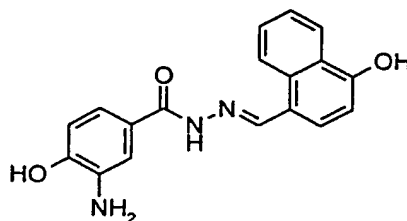
4-Hydroxybenzoic acid (benzylidene)hydrazide



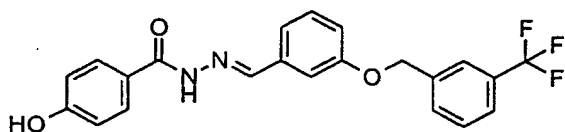
4-Hydroxybenzoic acid (1-naphthylmethylene)hydrazide



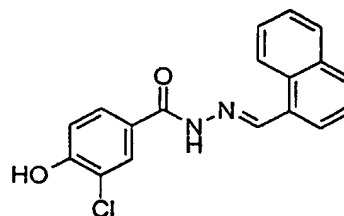
3-Amino-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide



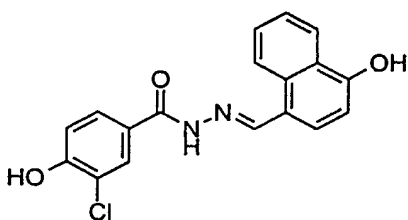
3-Amino-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



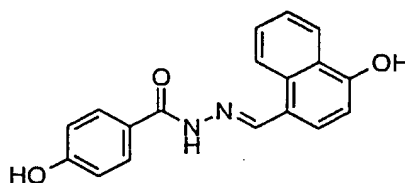
4-Hydroxybenzoic acid [3-(3-trifluoromethylbenzyloxy)benzylidene]hydrazide



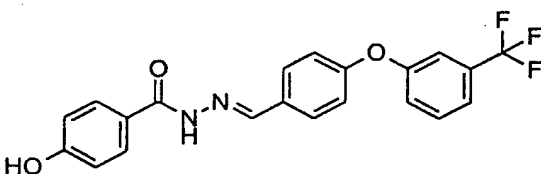
3-Chloro-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide



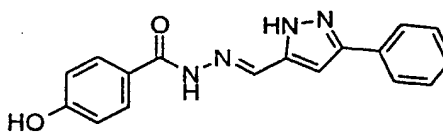
3-Chloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



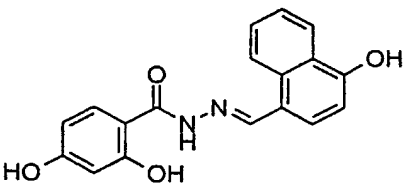
4-Hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



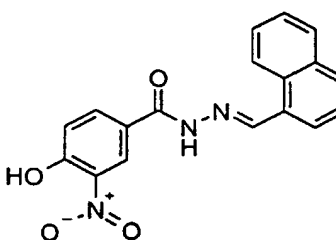
4-Hydroxybenzoic acid [4-(3-trifluoromethylphenoxy)benzylidene]hydrazide



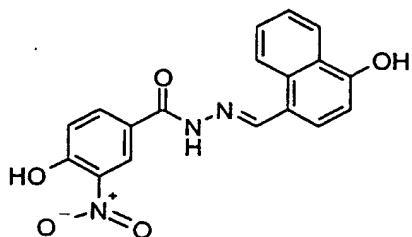
4-Hydroxybenzoic acid (5-phenyl-3-pyrazolylmethylene)hydrazide



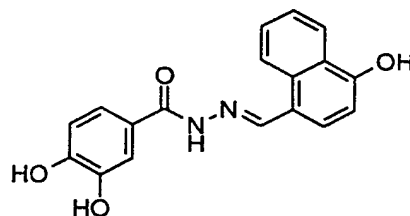
2,4-Dihydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



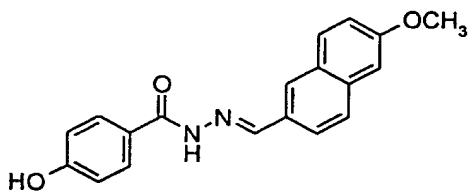
4-Hydroxy-3-nitrobenzoic acid (1-naphthylmethylene)hydrazide



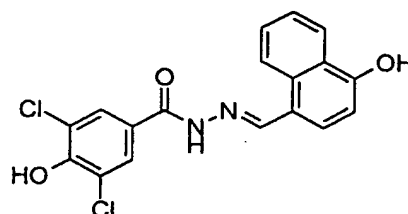
4-Hydroxy-3-nitrobenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



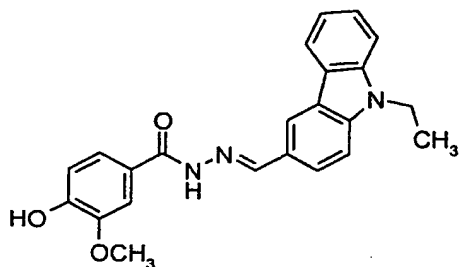
3,4-Dihydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



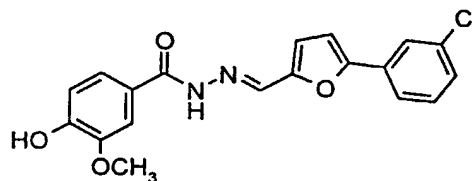
4-Hydroxybenzoic acid (6-methoxy-2-naphthylmethylene)hydrazide



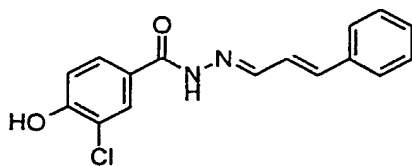
3,5-Dichloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



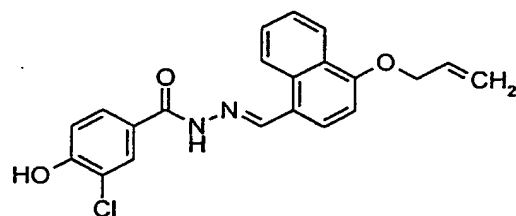
4-Hydroxy-3-methoxybenzoic acid (9-ethyl-9H-3-carbazolylmethylene)hydrazide



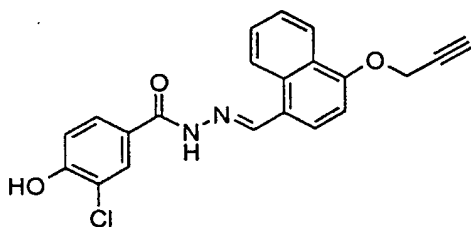
4-Hydroxy-3-methoxybenzoic acid [5-(3-chlorophenyl)-2-furanyl]methylene]hydrazide



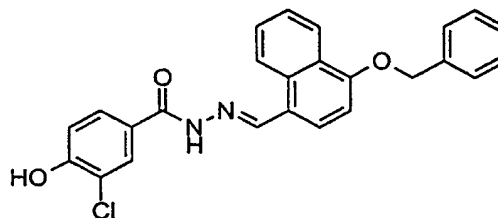
3-Chloro-4-hydroxybenzoic acid (3-phenyl-E-allylidene)hydrazide



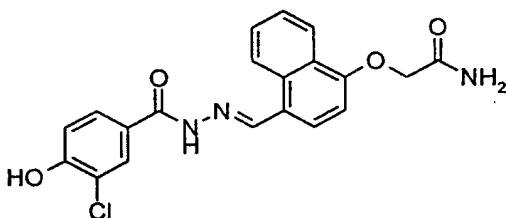
3-Chloro-4-hydroxybenzoic acid (4-allyloxy-1-naphthylmethylene)hydrazide



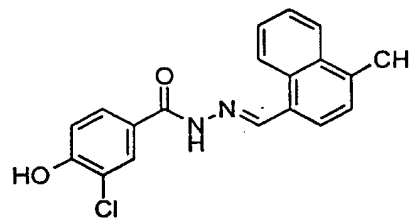
3-Chloro-4-hydroxybenzoic acid (4-ethynylmethoxy-1-naphthylmethylene)hydrazide



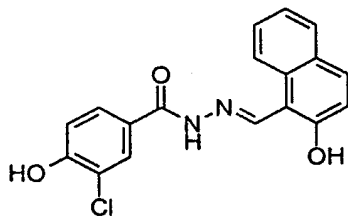
3-Chloro-4-hydroxybenzoic acid (4-benzyloxy-1-naphthylmethylene)hydrazide



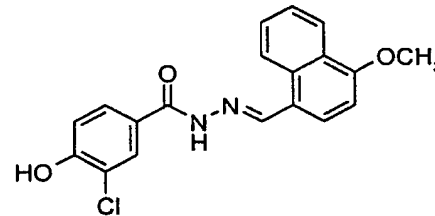
2-(4-[(3-Chloro-4-hydroxybenzoyl)hydrazono]methyl)-1-naphthoxyacetamide



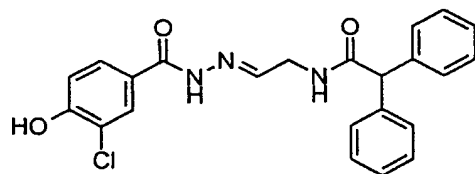
3-Chloro-4-hydroxybenzoic acid (4-methyl-1-naphthylmethylene)hydrazide



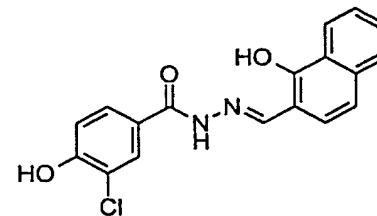
3-Chloro-4-hydroxybenzoic acid (2-hydroxy-1-naphthylmethylene)hydrazide



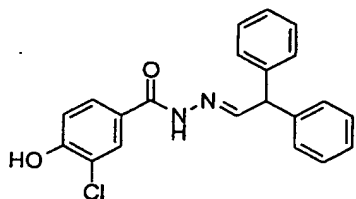
3-Chloro-4-hydroxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide



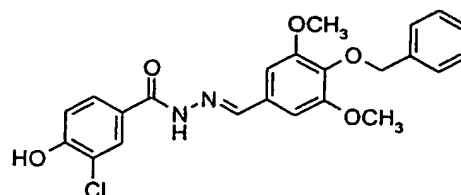
N-(2-[(3-Chloro-4-hydroxybenzoyl)hydrazono]ethyl)-2,2-diphenylacetamide



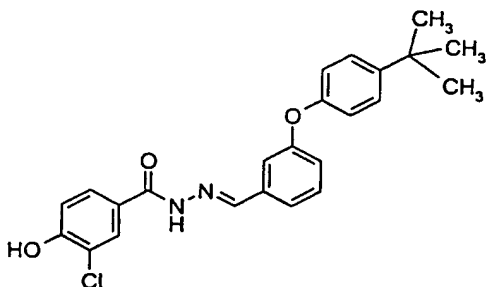
3-Chloro-4-hydroxybenzoic acid (1-hydroxy-2-naphthylmethylene)hydrazide



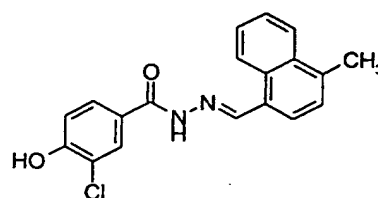
3-Chloro-4-hydroxybenzoic acid (2,2-diphenylethylidene)hydrazide



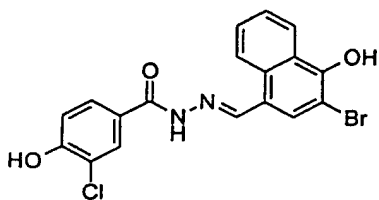
3-Chloro-4-hydroxybenzoic acid (4-benzyloxy-3,5-dimethoxybenzylidene)hydrazide



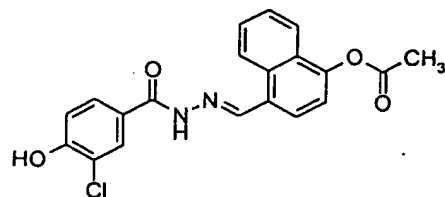
3-Chloro-4-hydroxybenzoic acid [3-(4-tert-butylphenoxy)benzylidene]hydrazide



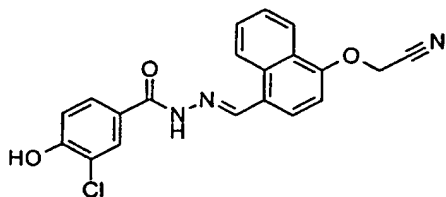
3-Chloro-4-hydroxybenzoic acid (4-methyl-1-naphthylmethylene)hydrazide



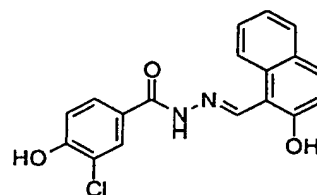
3-Chloro-4-hydroxybenzoic acid (3-bromo-4-hydroxy-1-naphthylmethylene)hydrazide



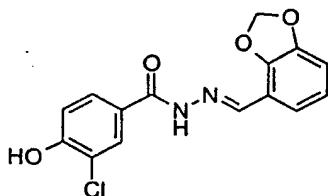
Acetic acid 4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyl ester



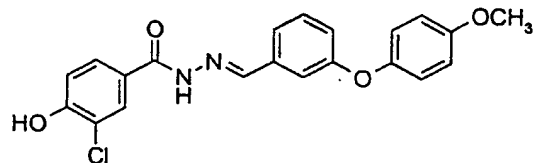
3-Chloro-4-hydroxybenzoic acid (4-cyanomethoxy-1-naphthylmethylene)hydrazide



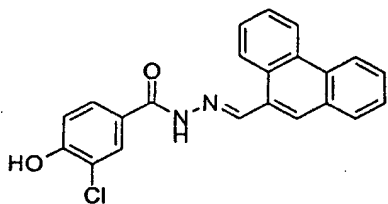
3-Chloro-4-hydroxybenzoic acid (2-hydroxy-1-naphthylmethylene)hydrazide



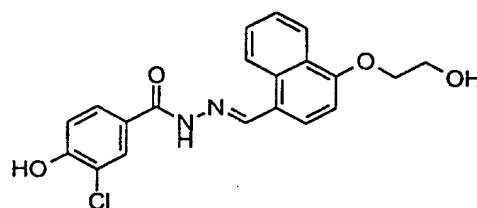
3-Chloro-4-hydroxybenzoic acid (2,3-methylenedioxybenzylidene)hydrazide



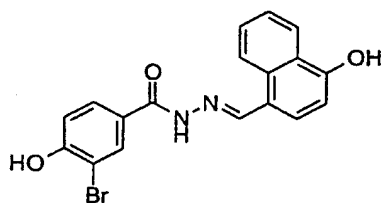
3-Chloro-4-hydroxybenzoic acid [3-(4-methoxyphenoxy)benzylidene]hydrazide



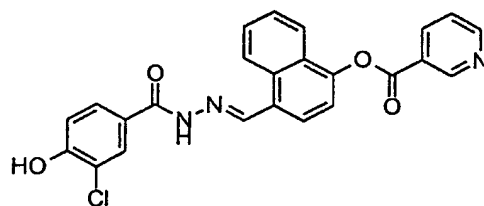
3-Chloro-4-hydroxybenzoic acid (9-phenanthrenylmethylene)hydrazide



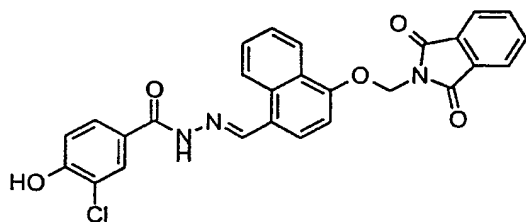
3-Chloro-4-hydroxybenzoic acid [4-(2-hydroxyethoxy)-1-naphthylmethylene]hydrazide



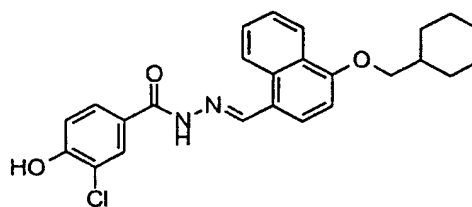
3-Bromo-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



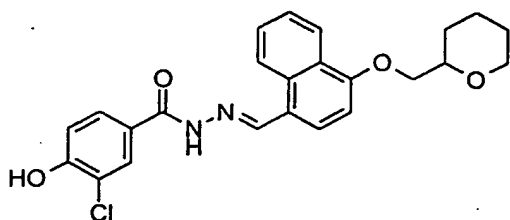
Nicotinic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyl ester



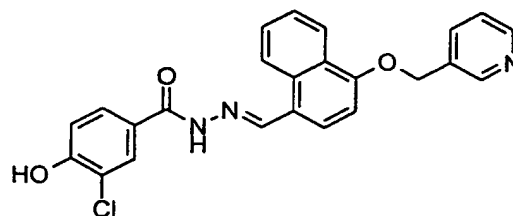
3-Chloro-4-hydroxybenzoic acid [4-(1,3-dioxo-1,3-dihydroisindol-2-ylmethoxy)-1-naphthylmethylene]hydrazide



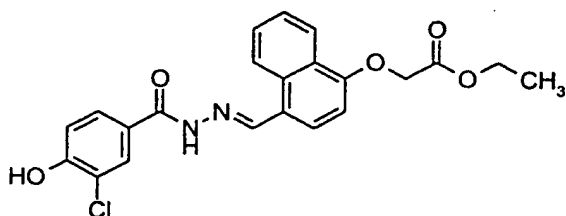
3-Chloro-4-hydroxybenzoic acid [4-(cyclohexylmethoxy)-1-naphthylmethylene]hydrazide



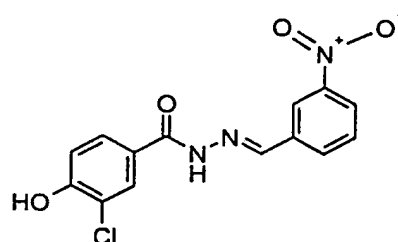
3-Chloro-4-hydroxybenzoic acid [4-(tetrahydro-2-pyranylmethoxy)-1-naphthylmethylene]hydrazide



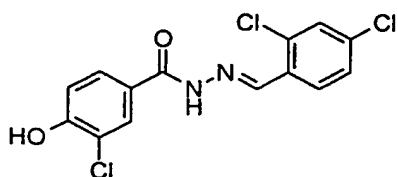
3-Chloro-4-hydroxybenzoic acid [4-(3-pyridylmethoxy)-1-naphthylmethylene]hydrazide



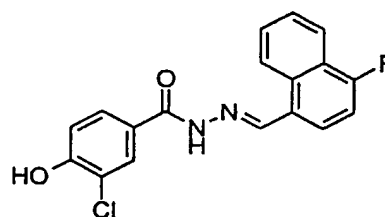
4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyloxy)acetic acid ethyl ester



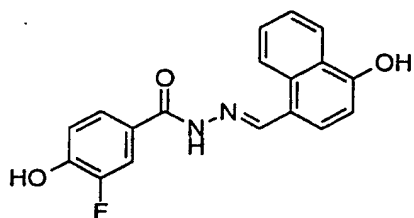
3-Chloro-4-hydroxybenzoic acid (3-nitrobenzylidene)hydrazide



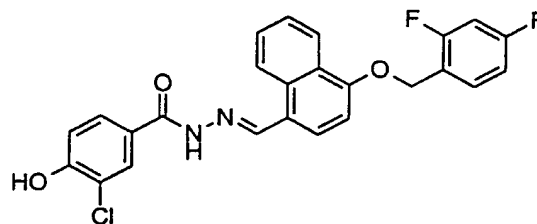
3-Chloro-4-hydroxybenzoic acid (2,4-dichlorobenzylidene)hydrazide



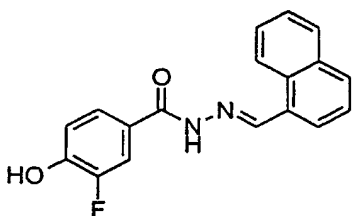
3-Chloro-4-hydroxybenzoic acid (4-fluoro-1-naphthylmethylene)hydrazide



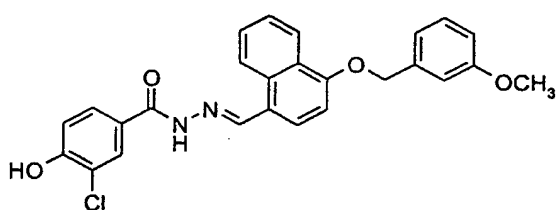
3-Fluoro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



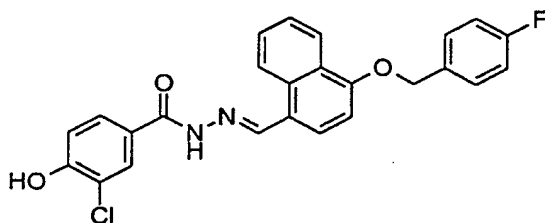
3-Chloro-4-hydroxybenzoic acid [4-(2,4-difluorobenzoyloxy)-1-naphthylmethylene]hydrazide



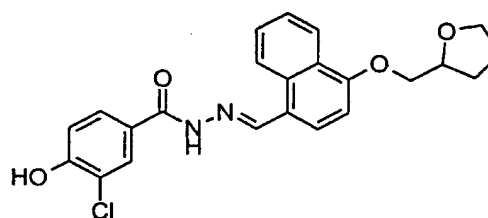
3-Fluoro-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide



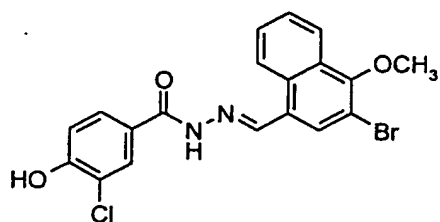
3-Chloro-4-hydroxybenzoic acid [4-(3-methoxybenzyloxy)-1-naphthylmethylene]hydrazide



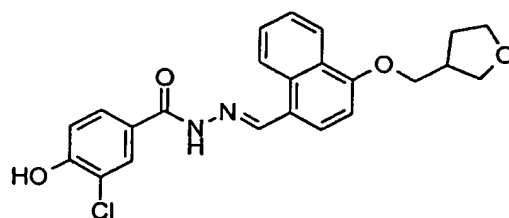
3-Chloro-4-hydroxybenzoic acid [4-(4-fluorobenzoyloxy)-1-naphthylmethylene]hydrazide



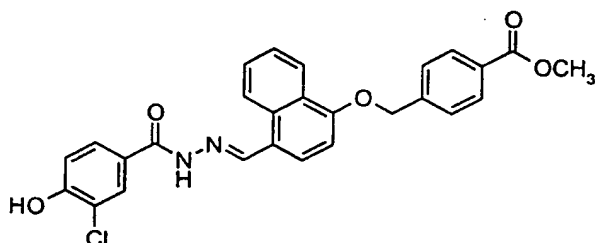
3-Chloro-4-hydroxybenzoic acid [4-(2-tetrahydrofuranylmethoxy)-1-naphthylmethylene]hydrazide



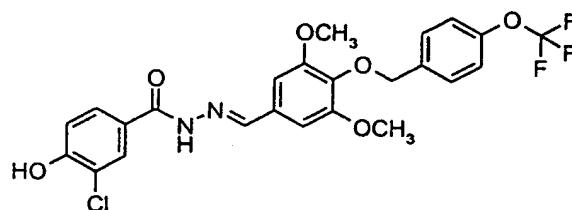
3-Chloro-4-hydroxybenzoic acid (3-bromo-4-methoxy-1-naphthylmethylene)hydrazide



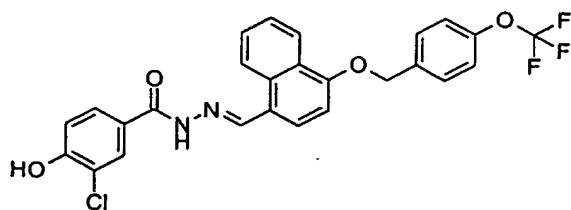
3-Chloro-4-hydroxybenzoic acid [4-(3-tetrahydrofuranylmethoxy)-1-naphthylmethylene]hydrazide



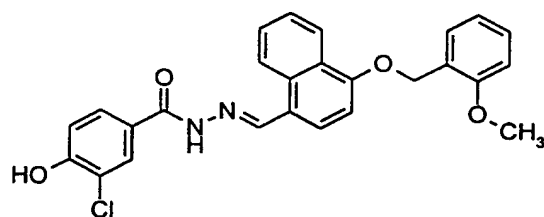
4-(4-[3-Chloro-4-hydroxybenzoyl]hydrazonomethyl)-1-naphthylmethyl benzoate methyl ester



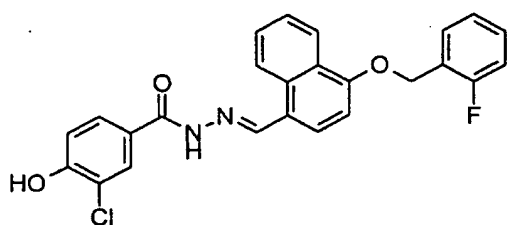
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-trifluoromethoxybenzyloxy)benzylidene]hydrazide



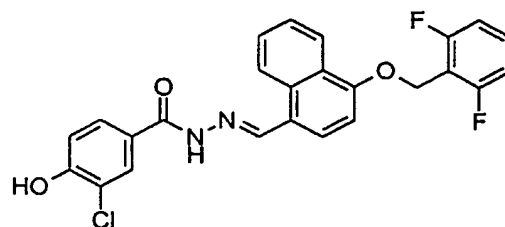
3-Chloro-4-hydroxybenzoic acid [4-(4-trifluoromethoxybenzyloxy)-1-naphthylmethylene]hydrazide



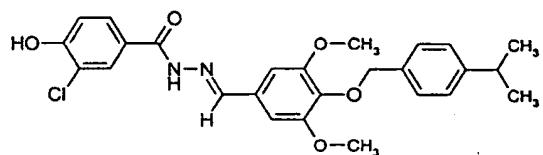
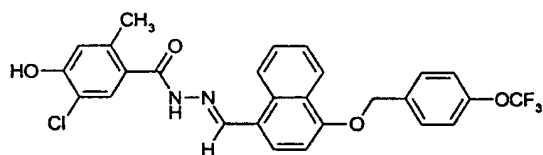
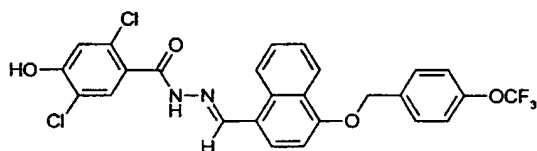
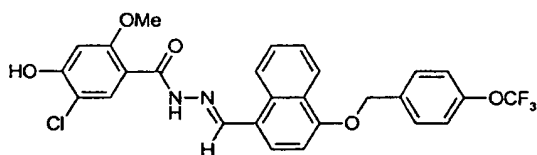
3-Chloro-4-hydroxybenzoic acid [4-(2-methoxybenzyloxy)-1-naphthylmethylene]hydrazide

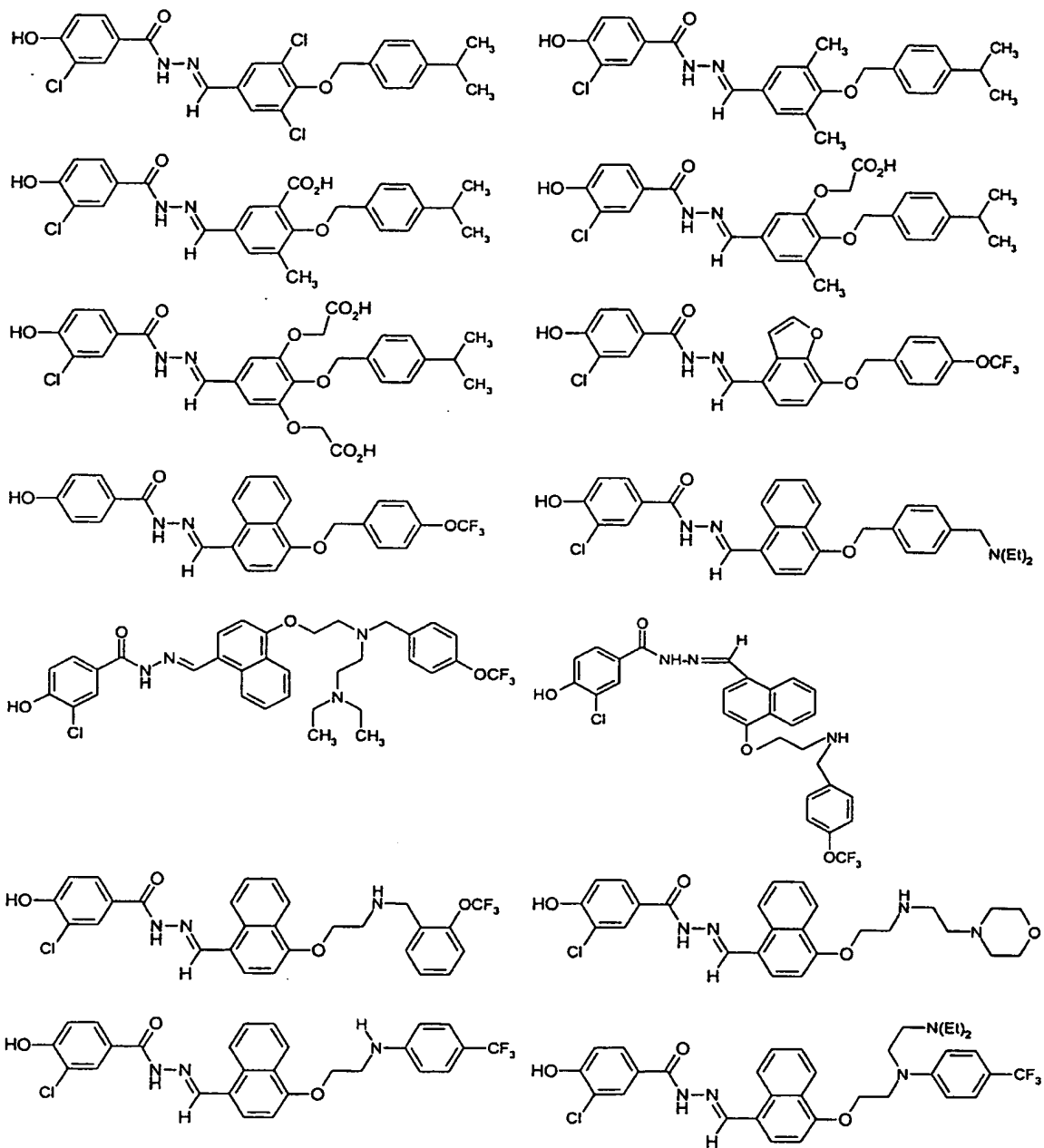


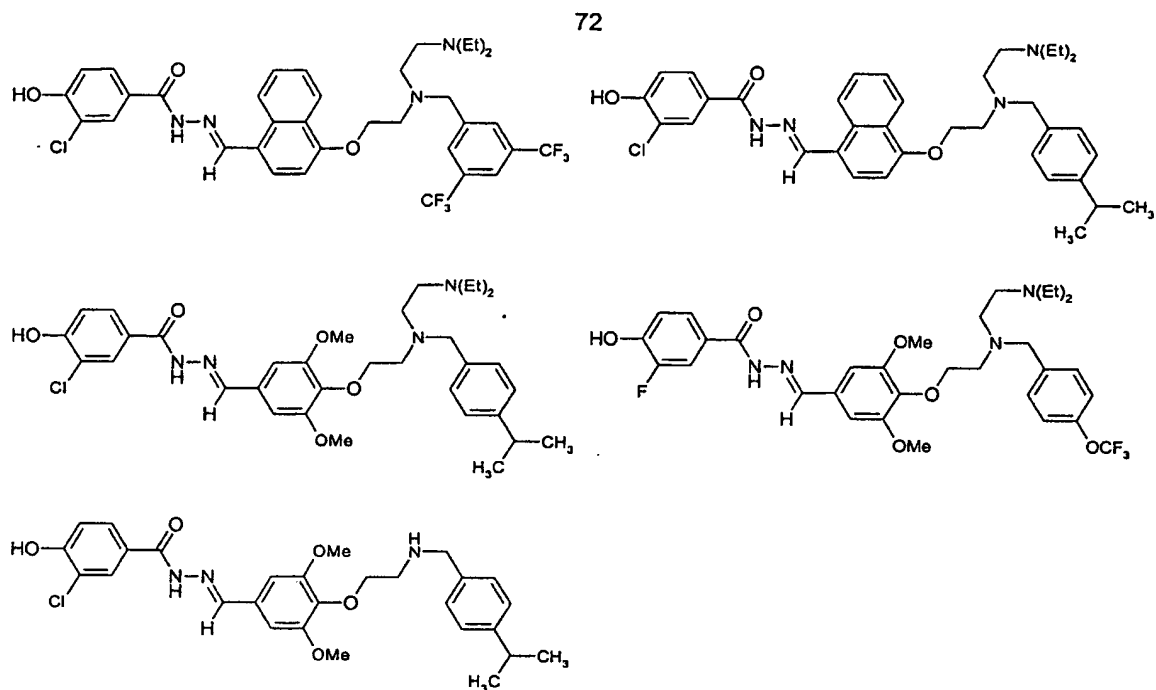
3-Chloro-4-hydroxybenzoic acid [4-(2-fluorobenzoyloxy)-1-naphthylmethylene]hydrazide



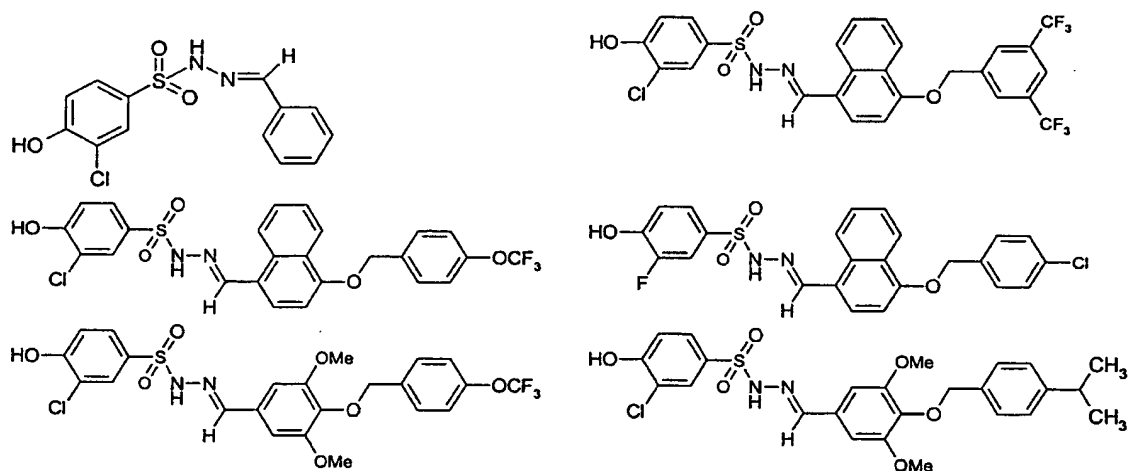
3-Chloro-4-hydroxybenzoic acid [4-(2,6-difluorobenzoyloxy)-1-naphthylmethylene]hydrazide





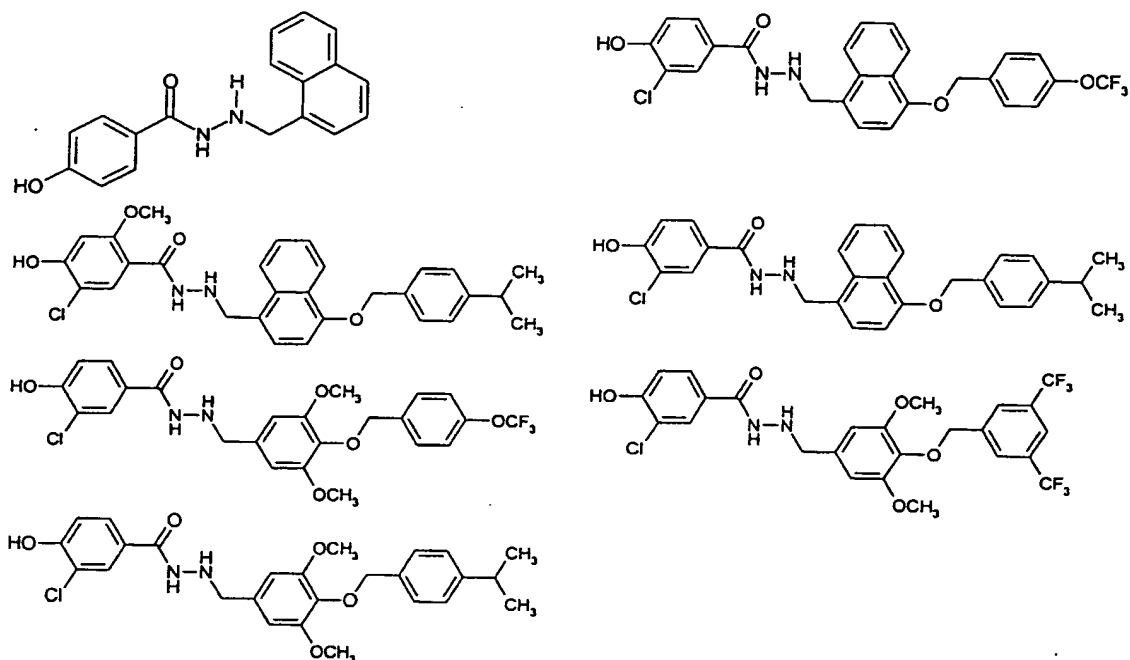


The most preferred specific compounds represented by the above general formula III are the following:

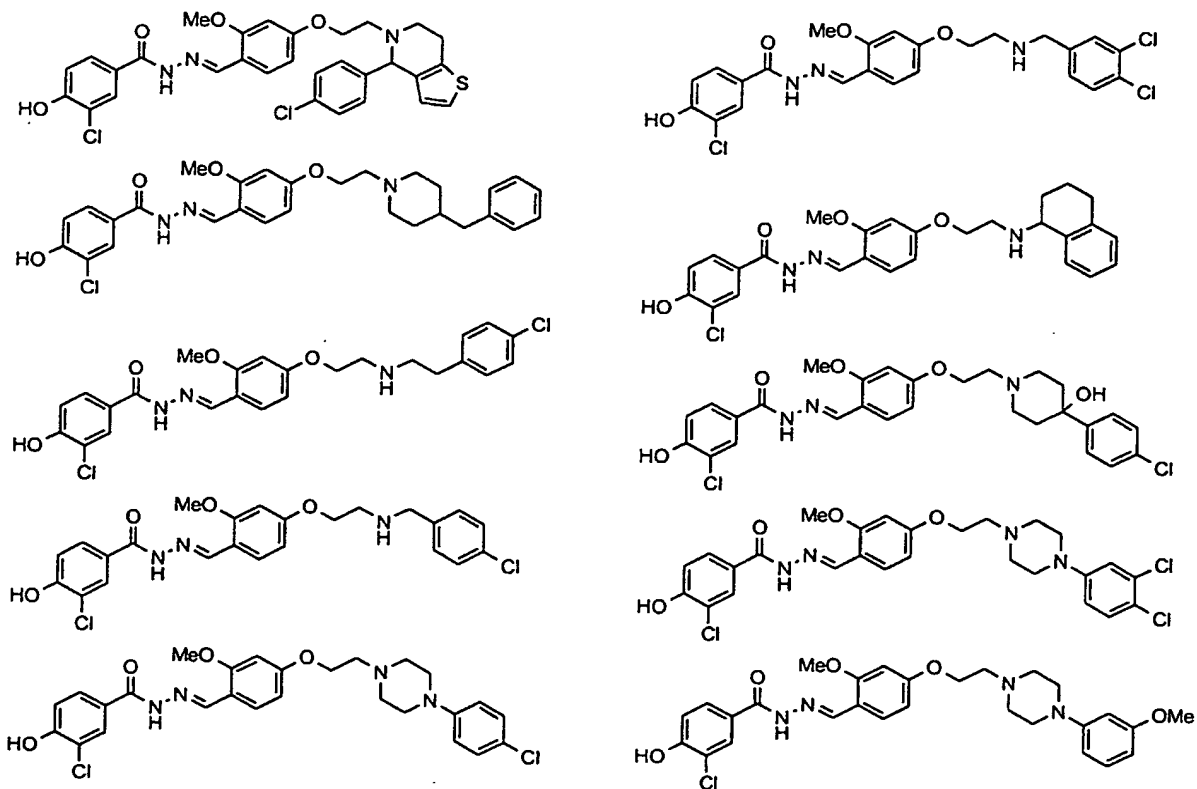


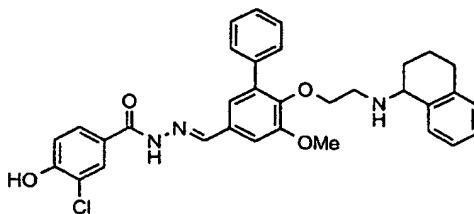
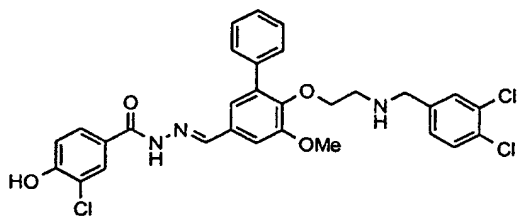
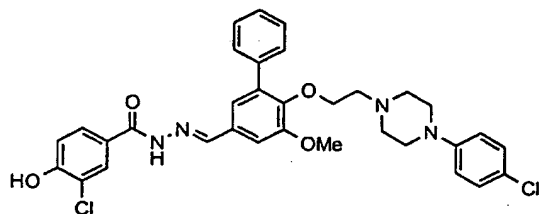
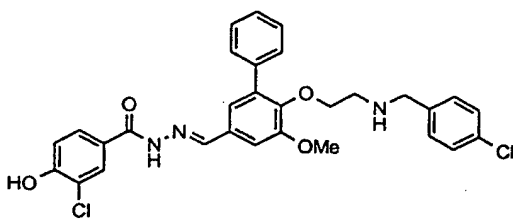
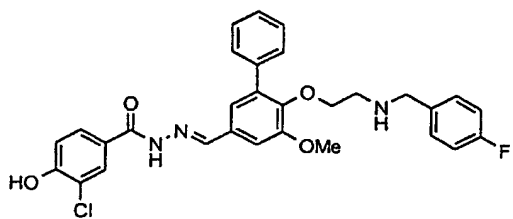
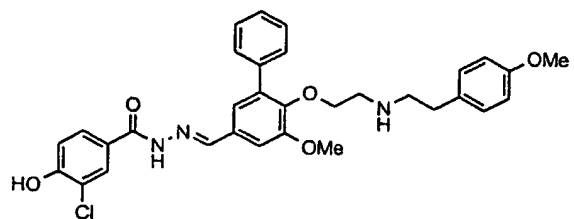
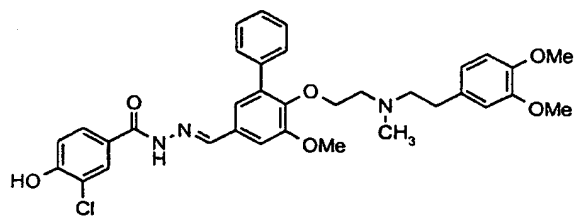
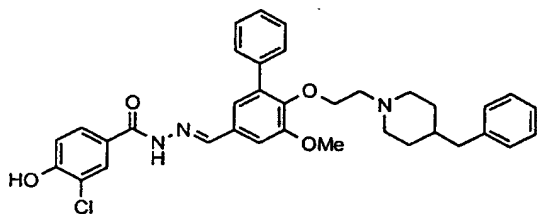
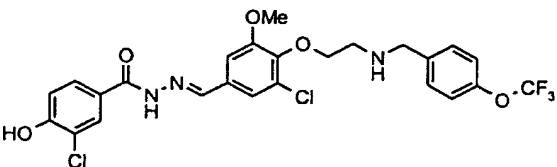
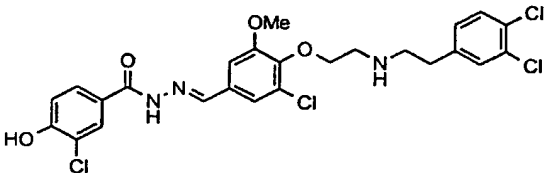
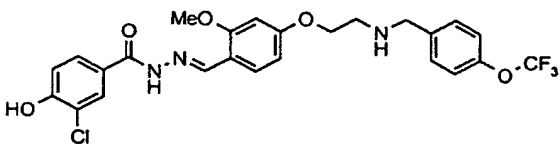
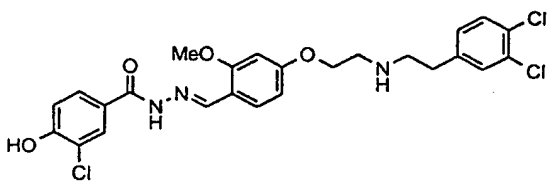
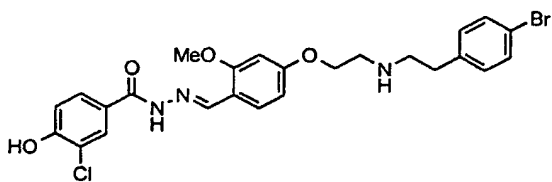
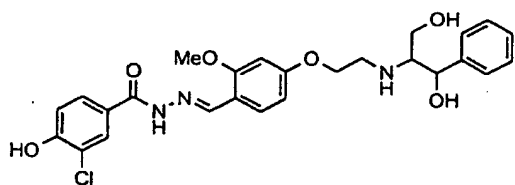
5 The most preferred specific compounds represented by the above general formula IV are the following:

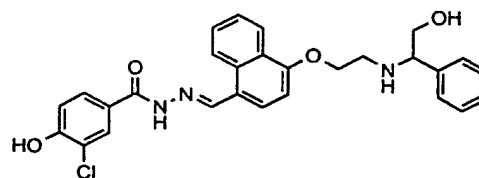
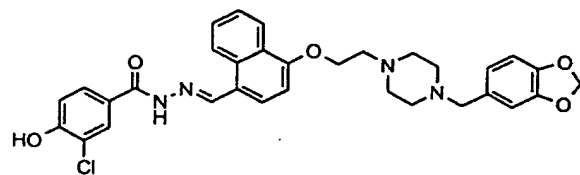
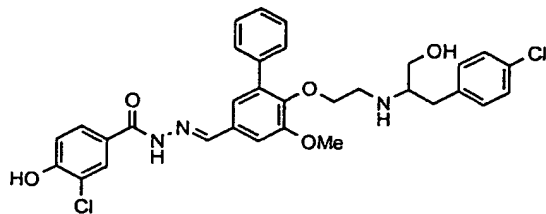
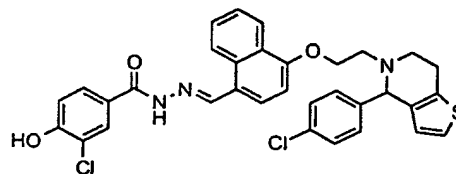
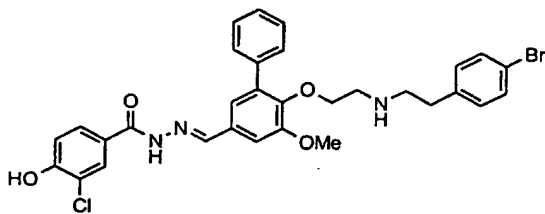
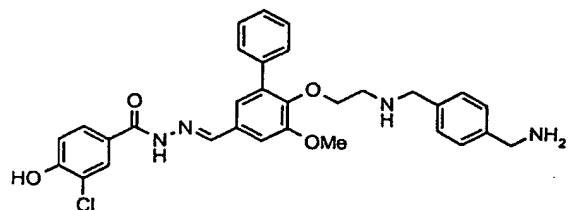
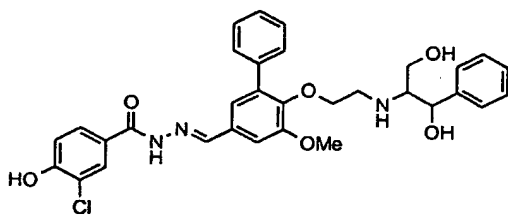
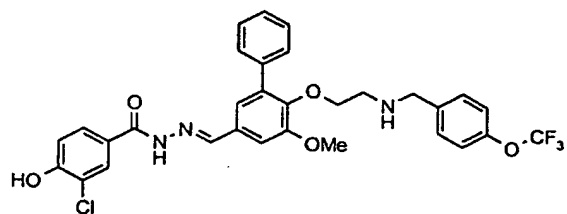
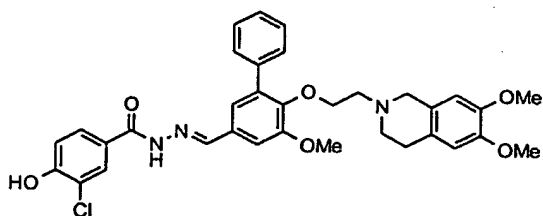
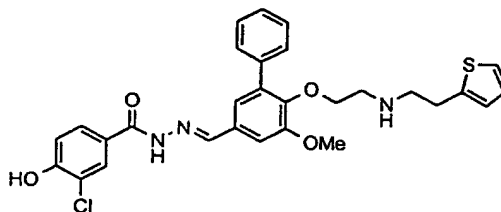
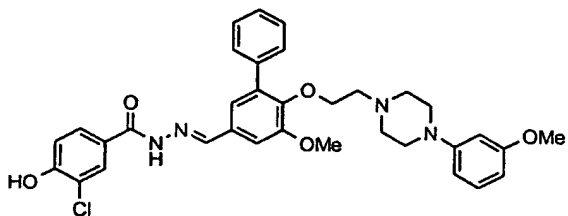
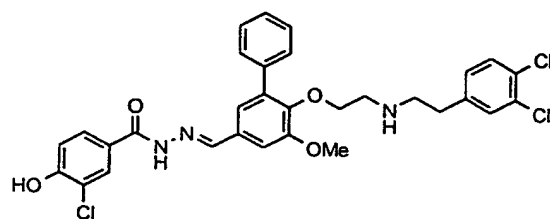
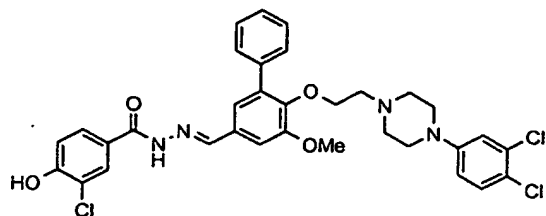
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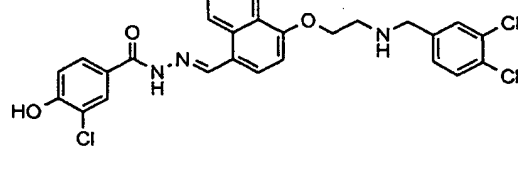
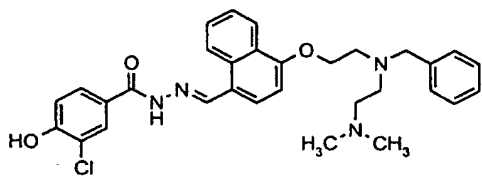
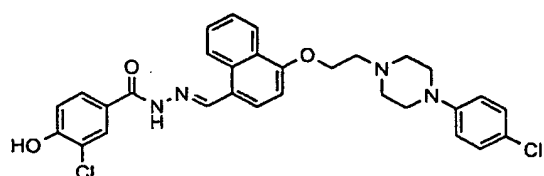
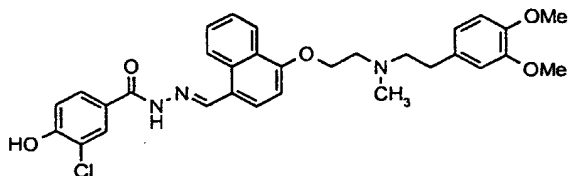
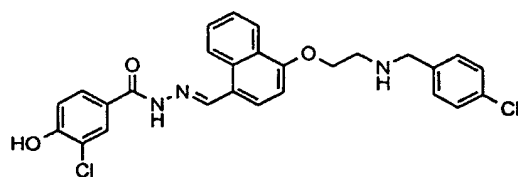
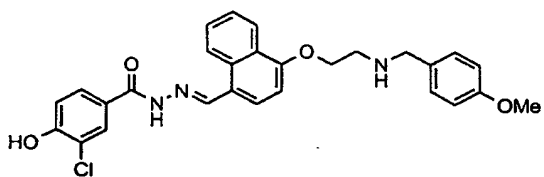
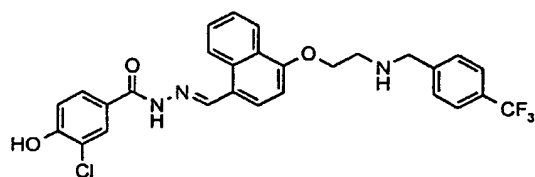
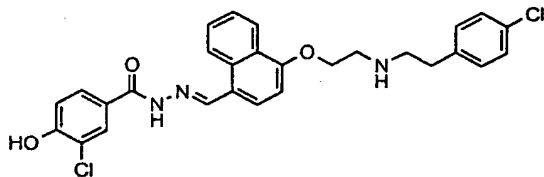
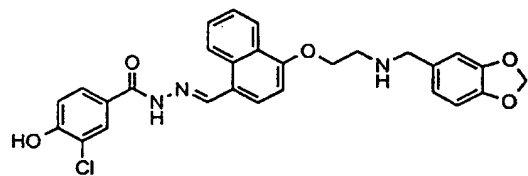
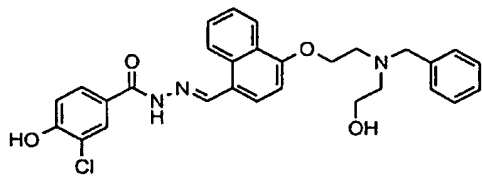
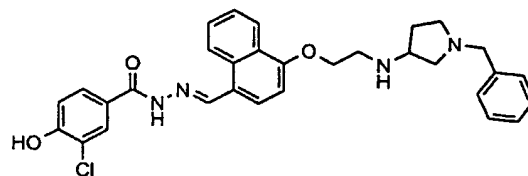
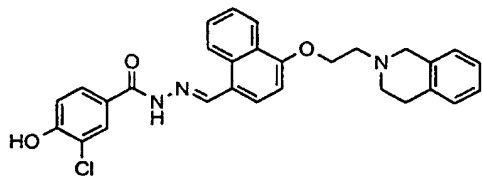
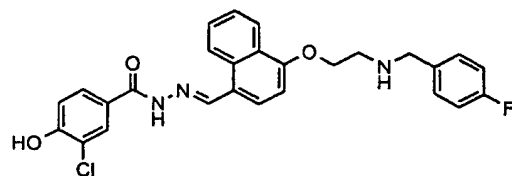
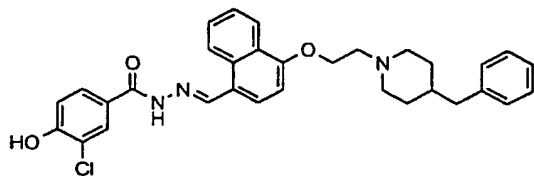
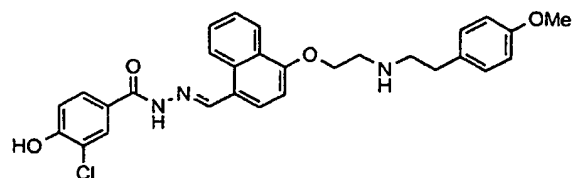
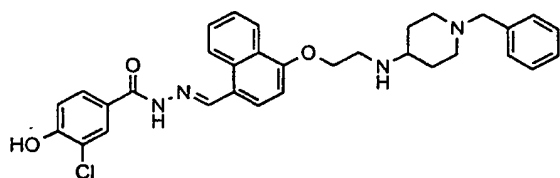


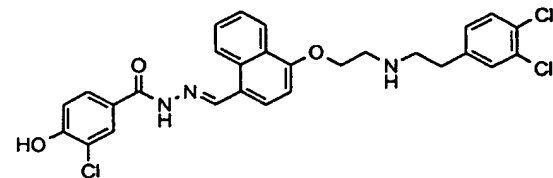
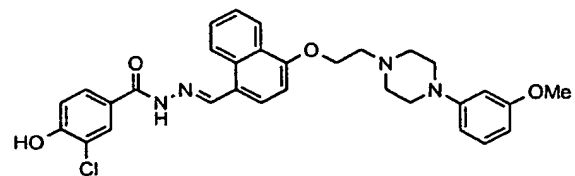
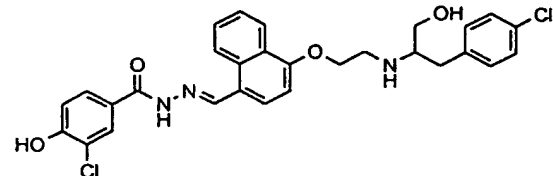
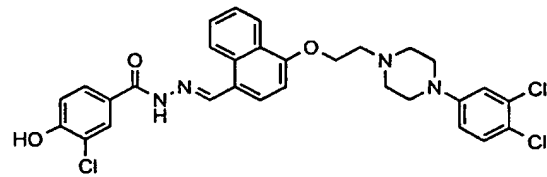
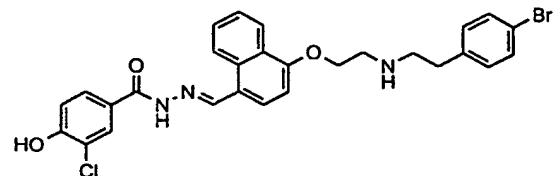
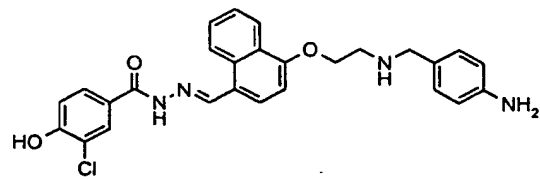
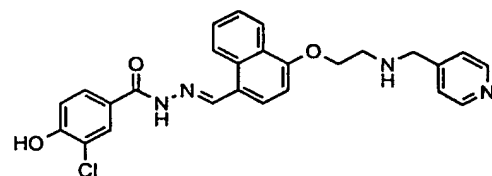
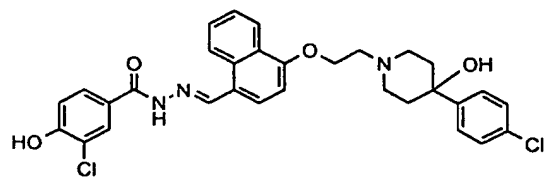
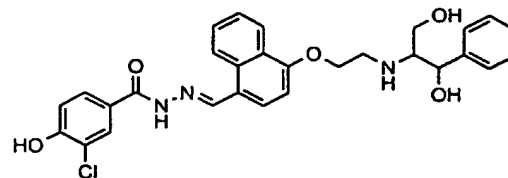
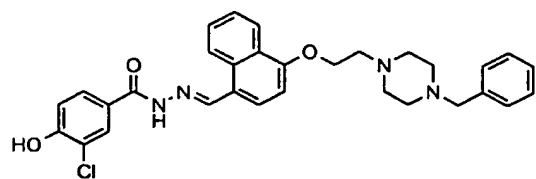
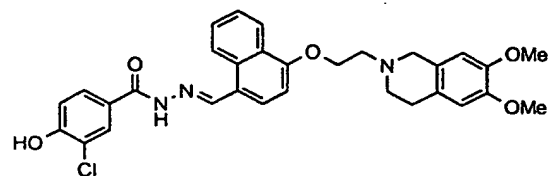
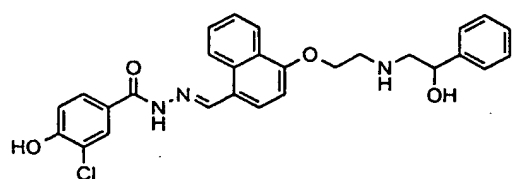
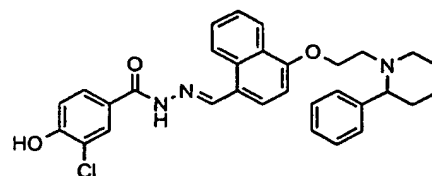
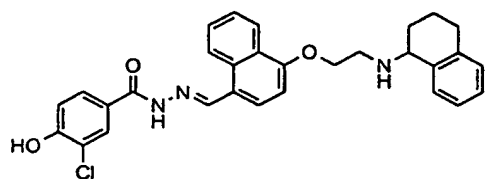
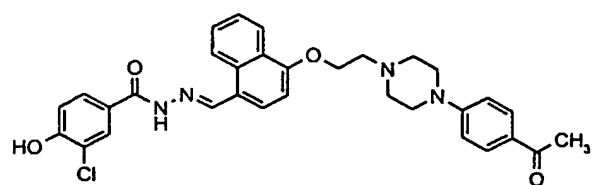
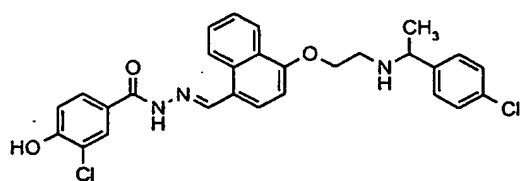
Preferred specific compounds represented by the formulae VI and VII are the following:

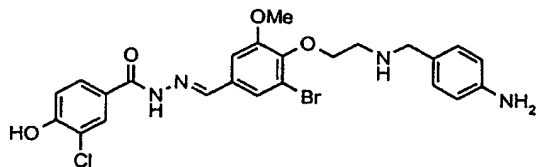
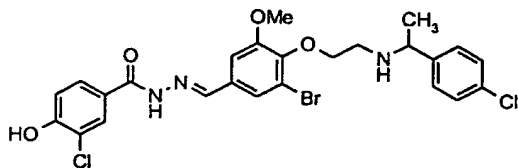
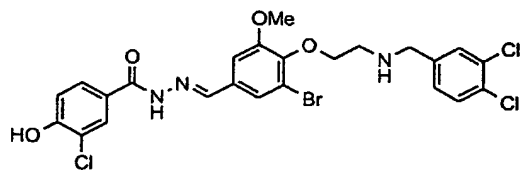
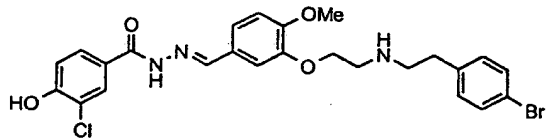
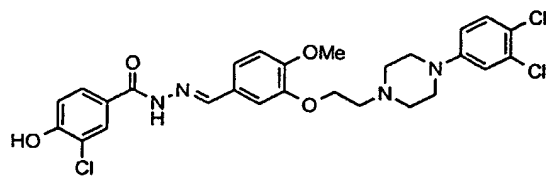
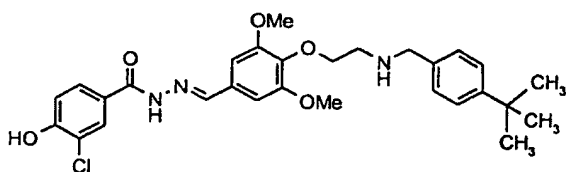
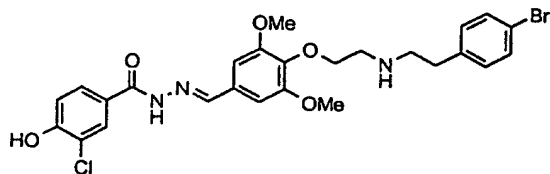
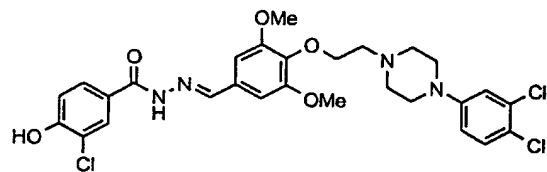
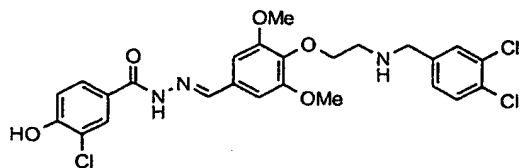
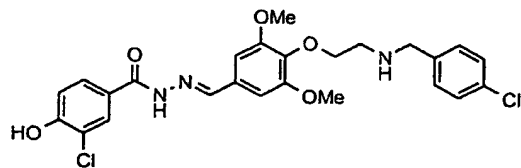
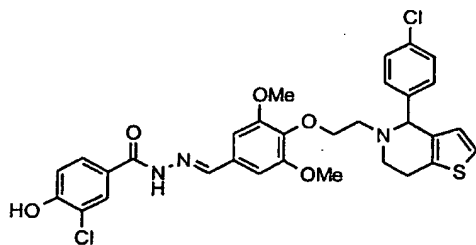
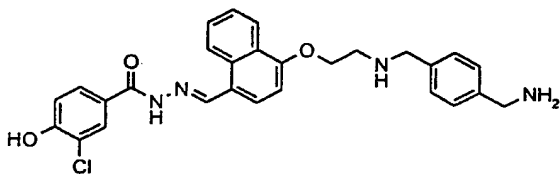
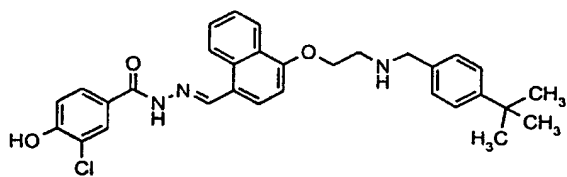
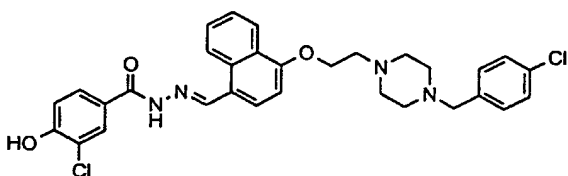
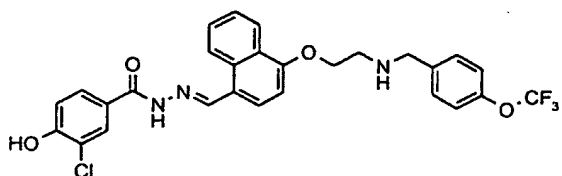
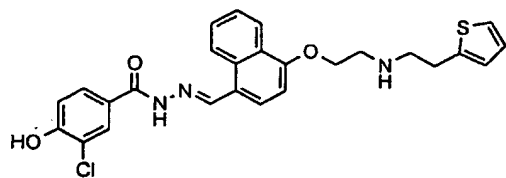


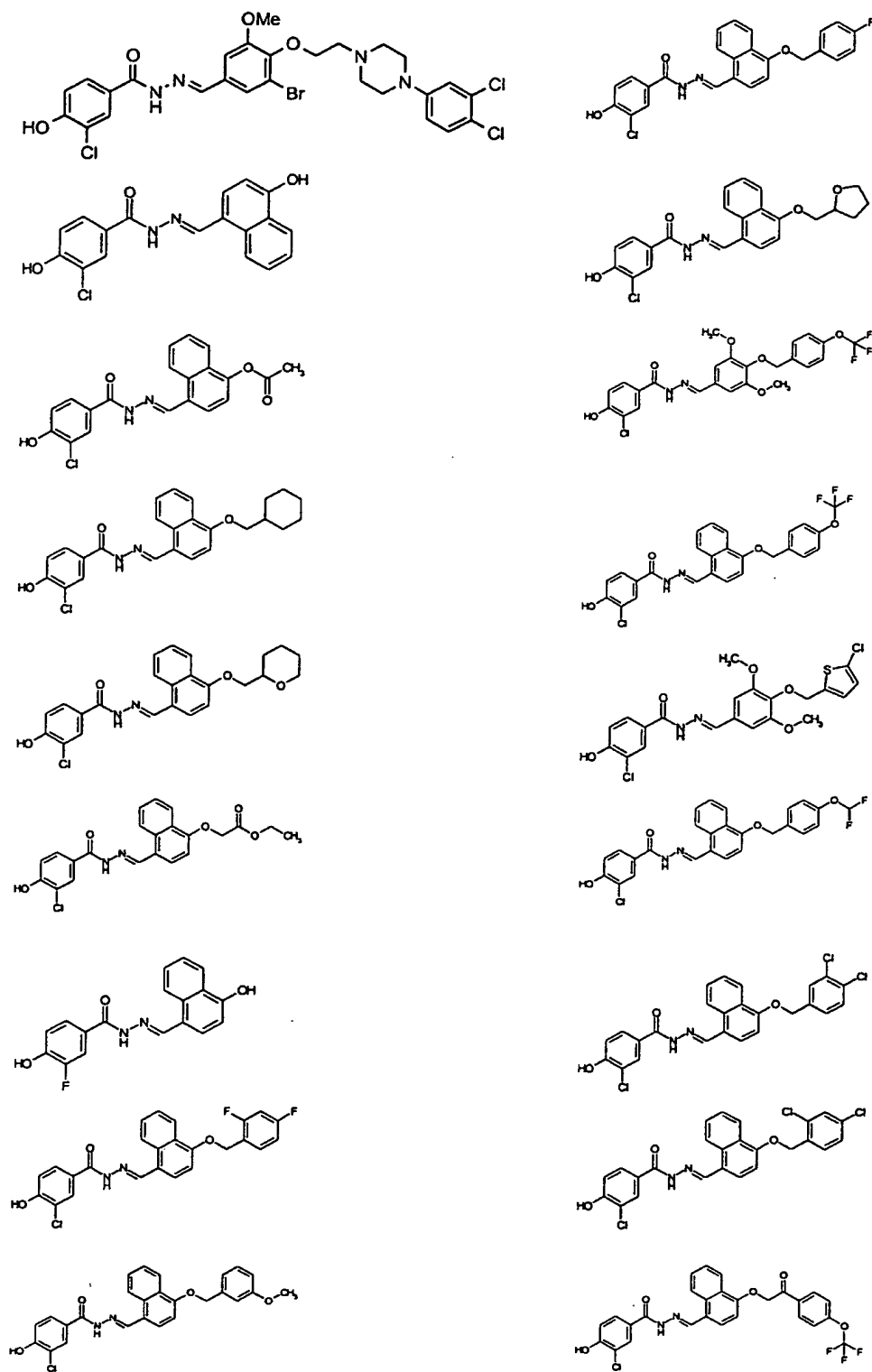


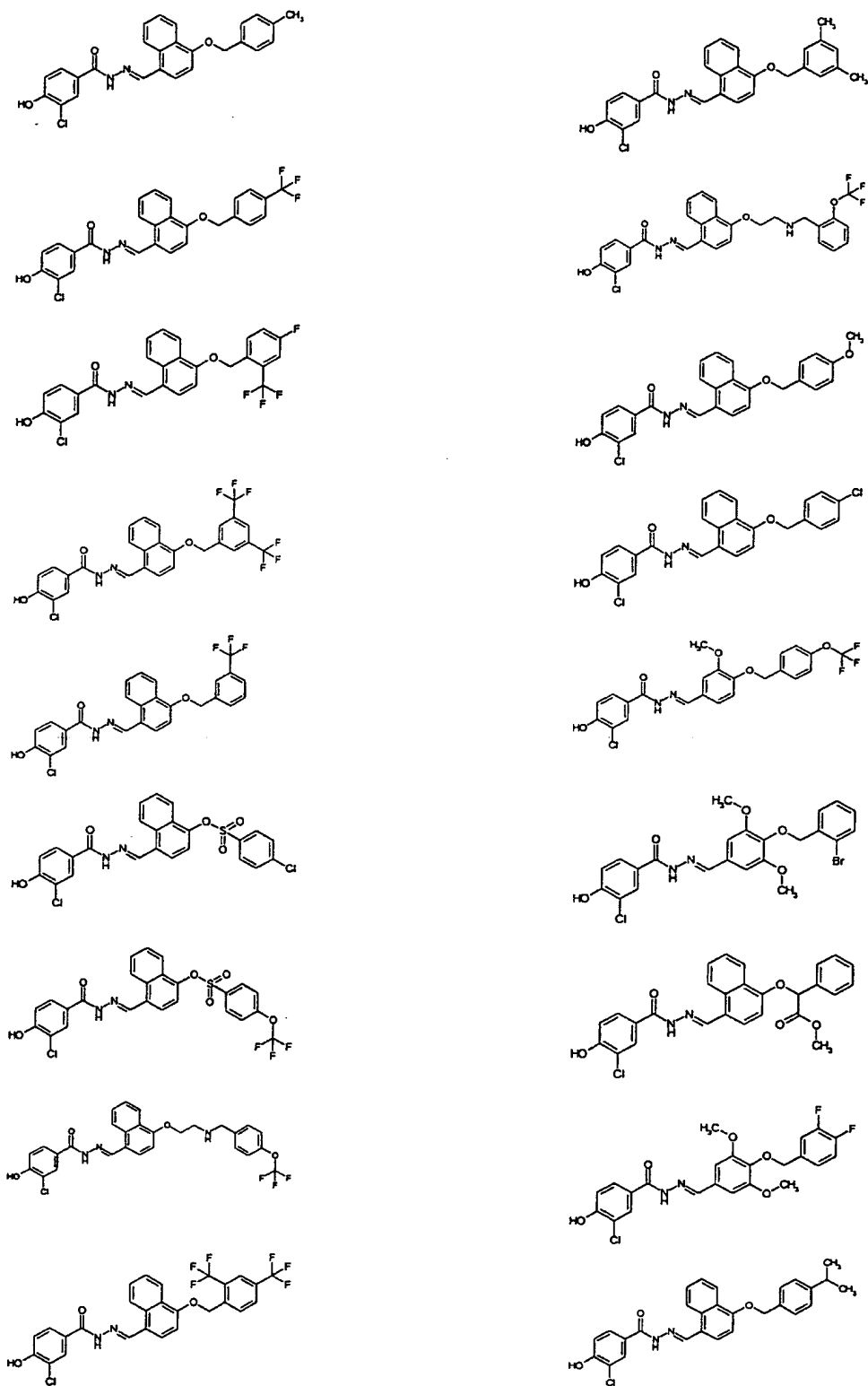


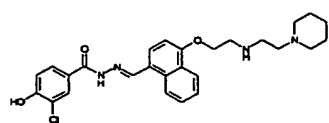
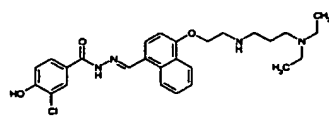
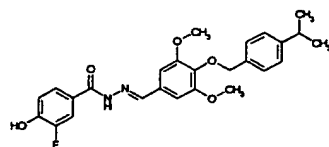
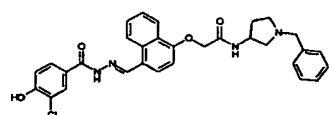
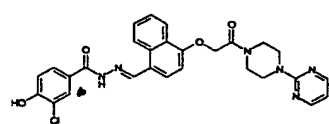
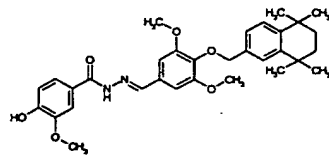
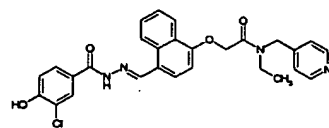
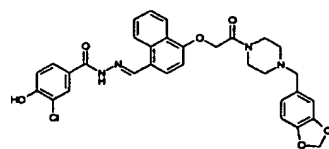
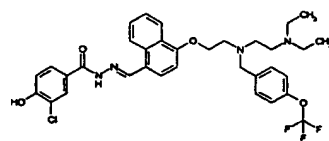
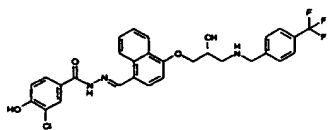
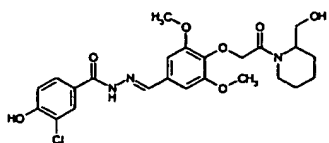
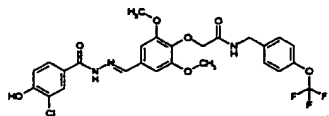
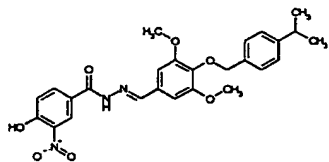
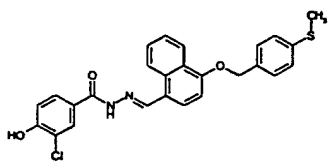
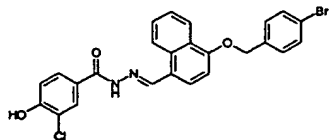
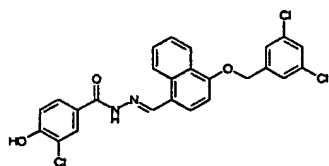
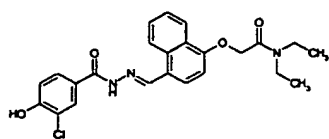
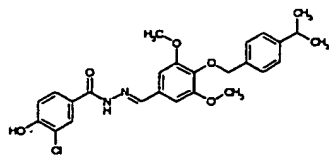


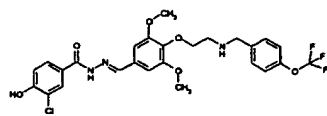
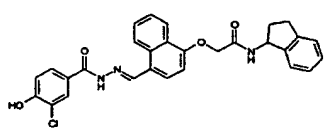
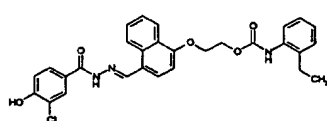
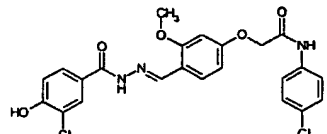
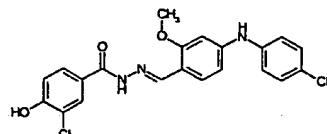
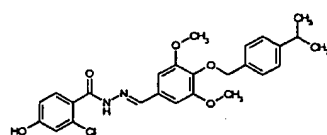
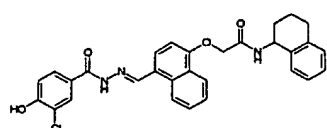
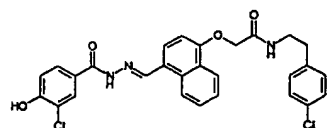
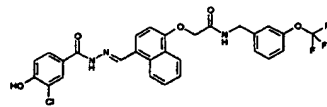
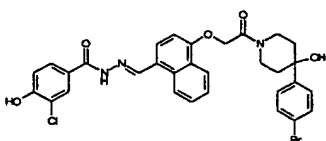
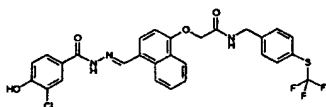
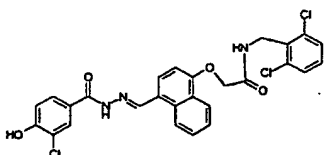
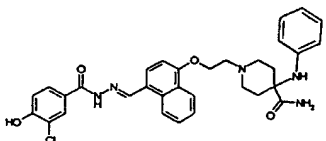
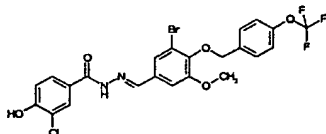
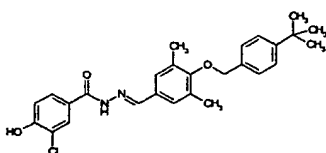
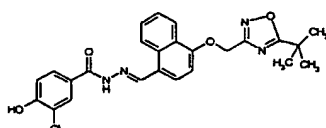
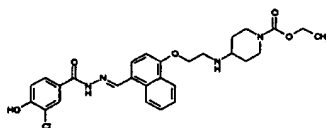
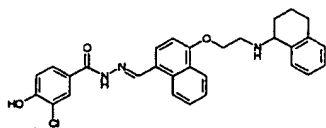


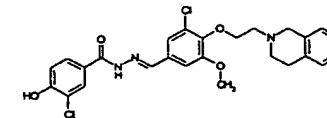
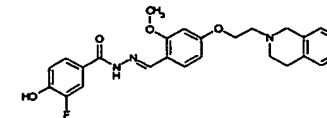
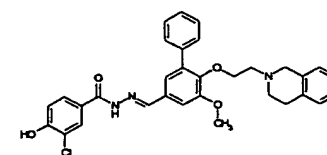
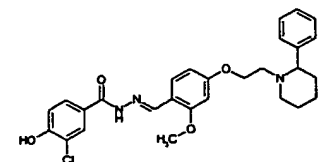
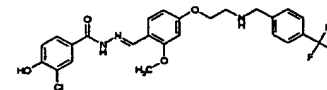
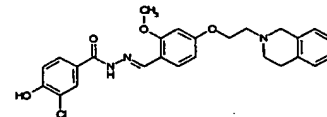
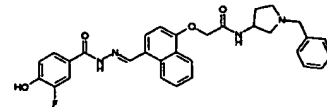
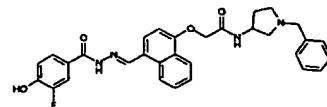
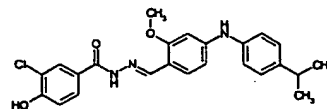
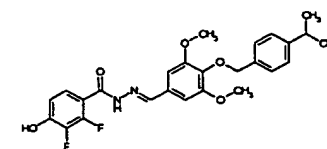
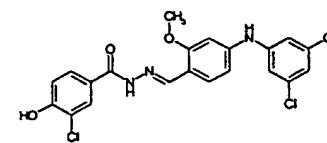
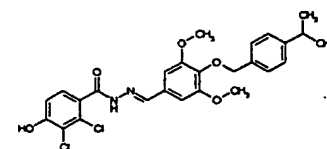
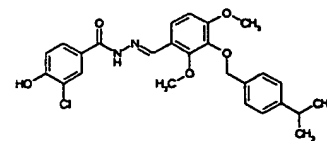
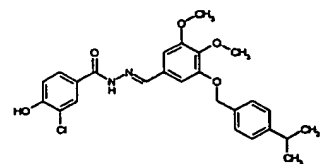
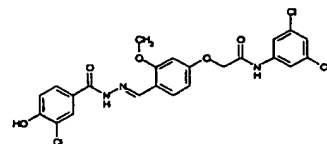
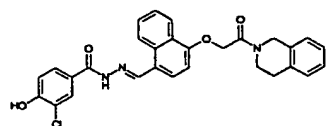
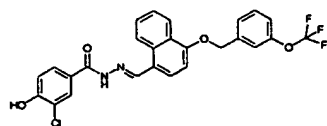
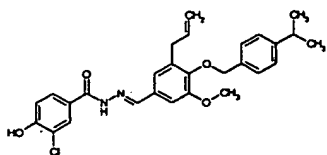




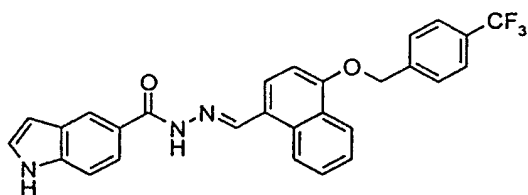




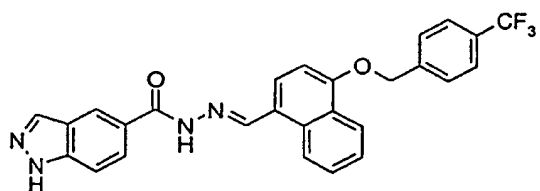




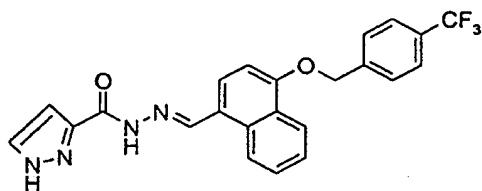
The most preferred specific compounds of formula I wherein A is a heterocyclic and/or bicyclic moiety are the following:



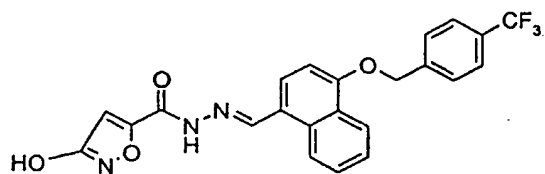
Indole-5-carboxylic acid [4-(4-trifluoromethylbenzyloxy)-1-naphthylmethylene]hydrazide



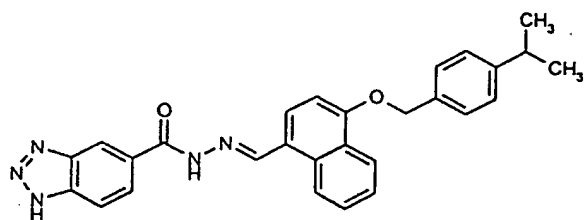
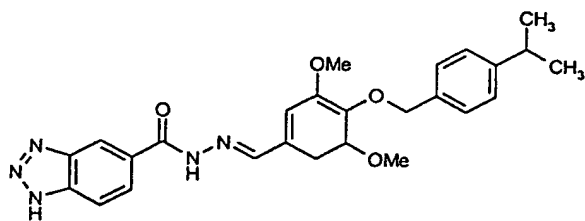
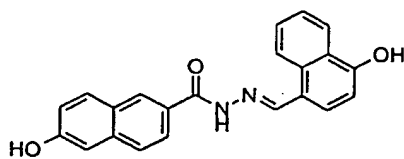
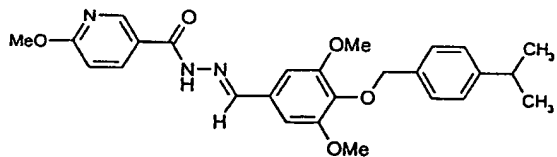
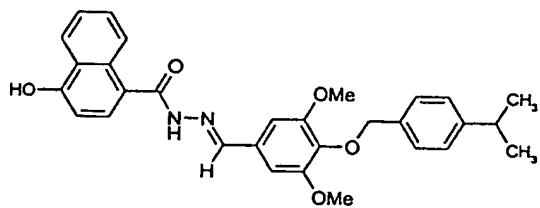
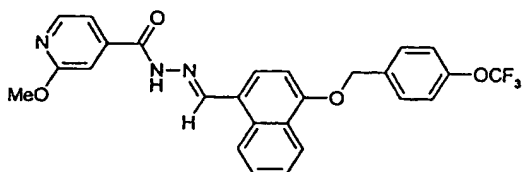
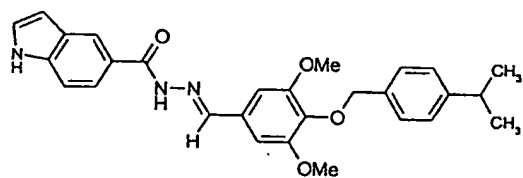
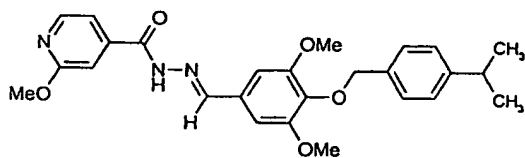
Indazole-5-carboxylic acid [4-(4-trifluoromethylbenzyloxy)-1-naphthylmethylene]hydrazide



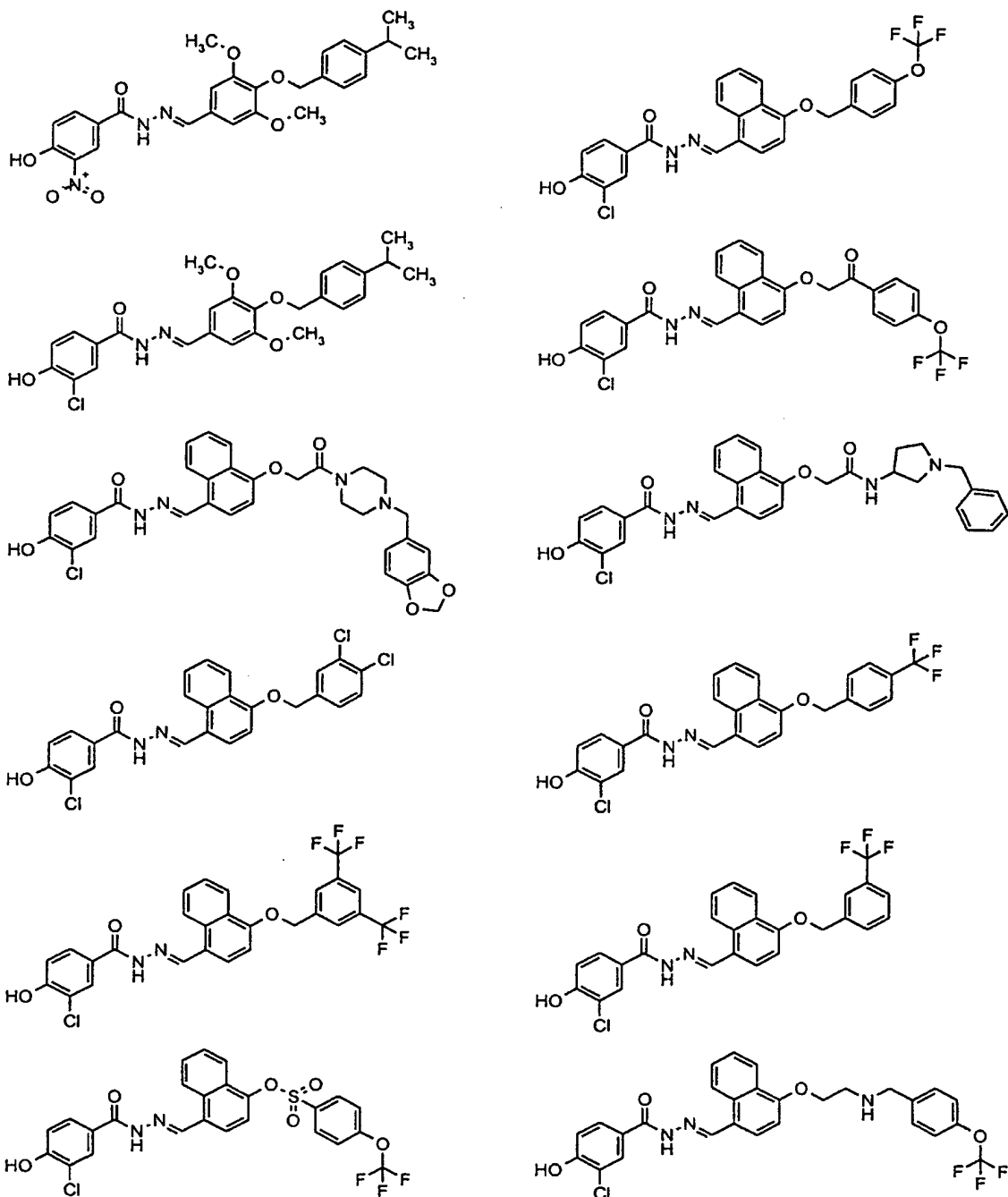
Pyrazole-3-carboxylic acid [4-(4-trifluoromethylbenzyloxy)-1-naphthylmethylene]hydrazide



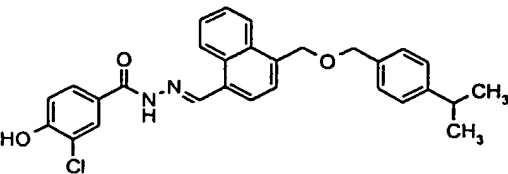
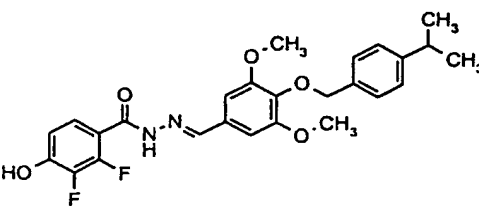
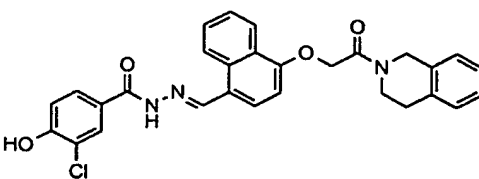
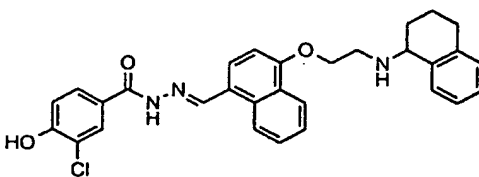
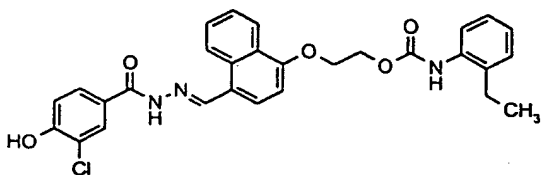
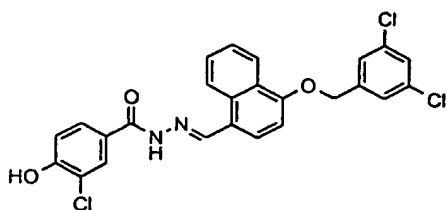
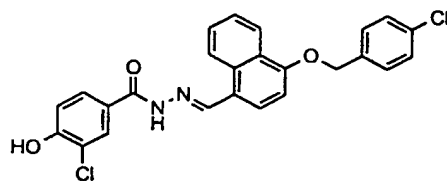
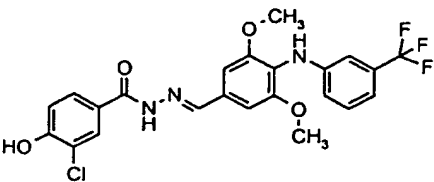
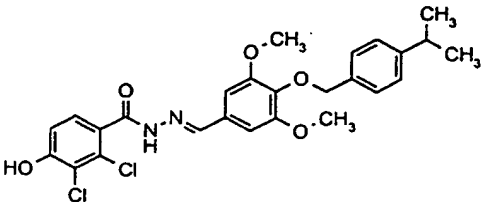
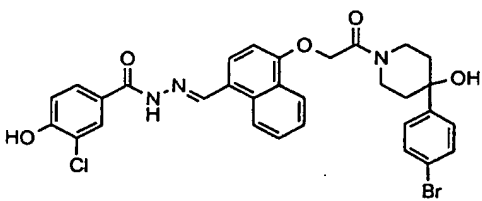
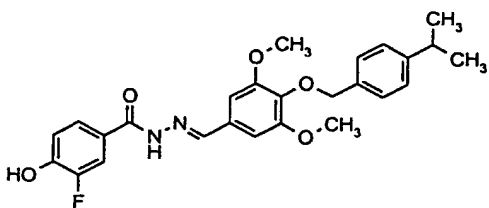
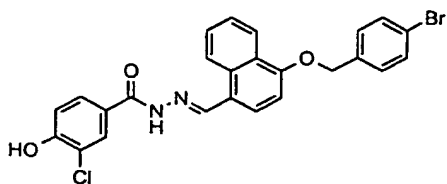
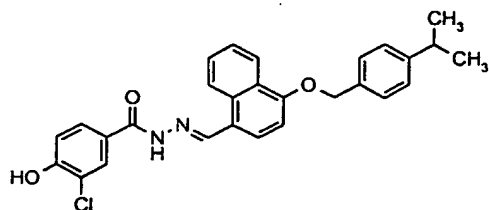
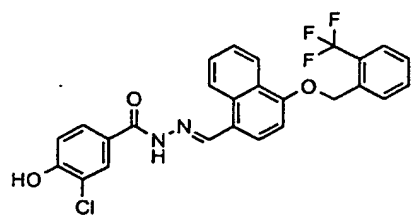
3-Hydroxyisoxazole-5-carboxylic acid [4-(4-trifluoromethylbenzyloxy)-1-naphthylmethylene]hydrazide



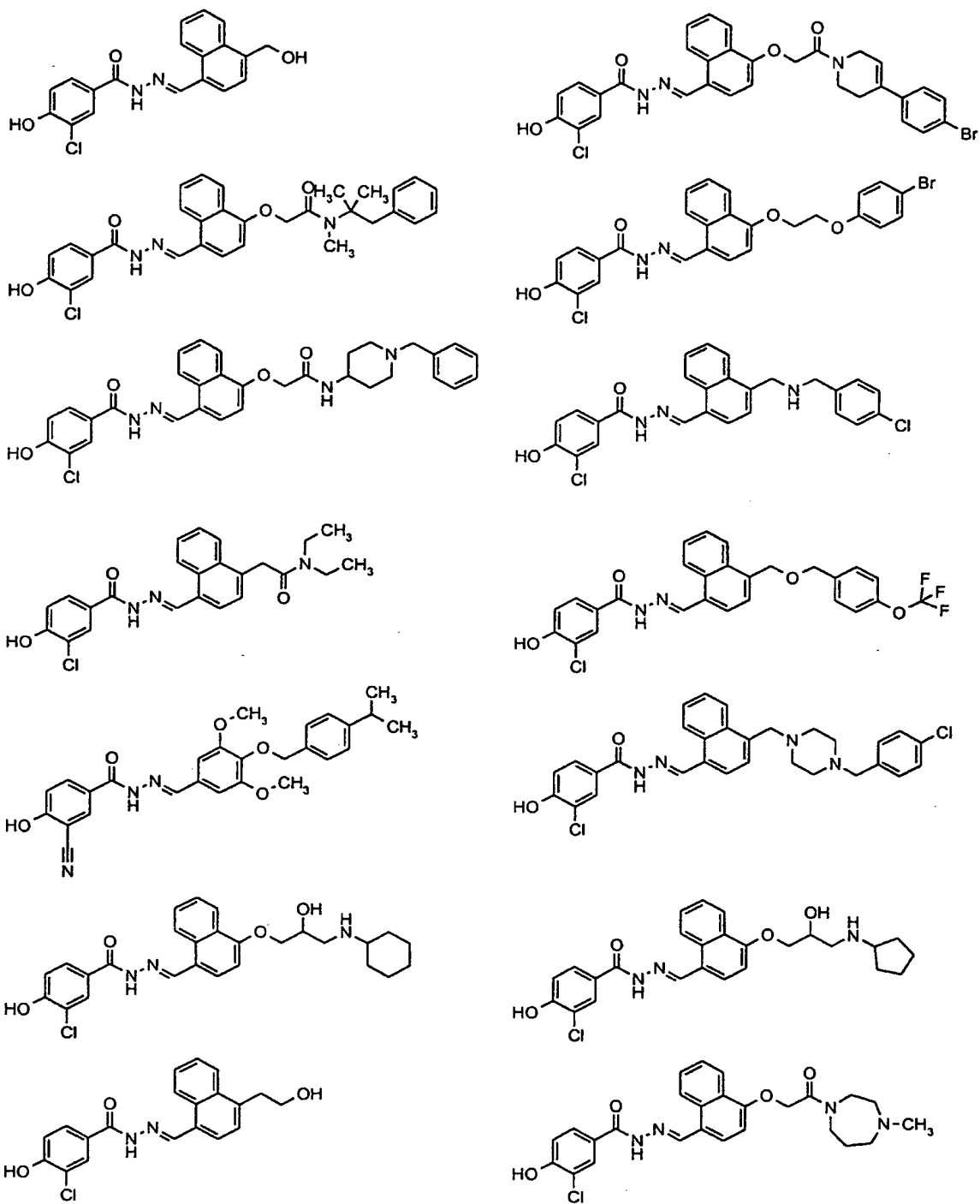
Especially preferred according to the present invention are the following compounds which show a particularly high affinity to the human glucagon receptor:

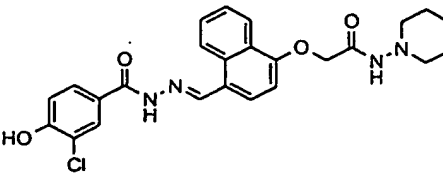
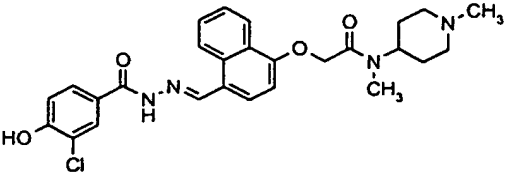
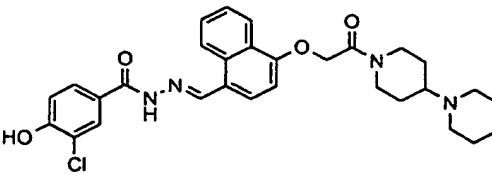
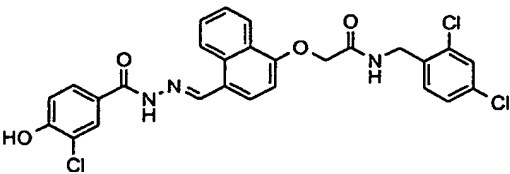
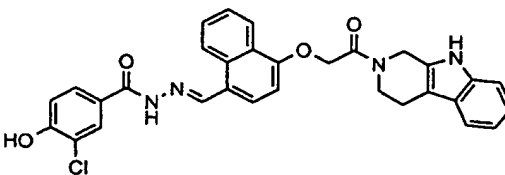
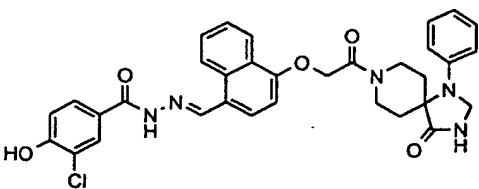
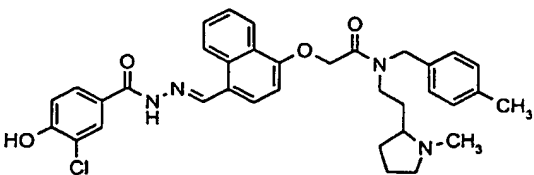
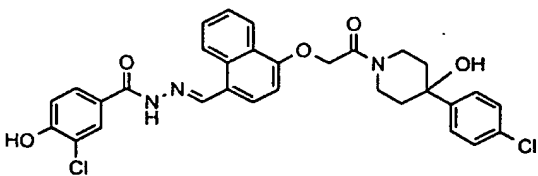
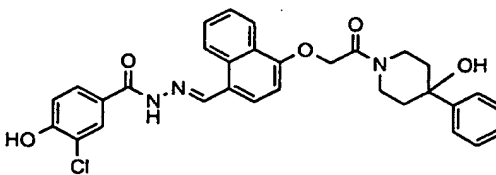
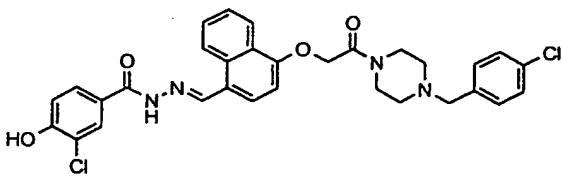
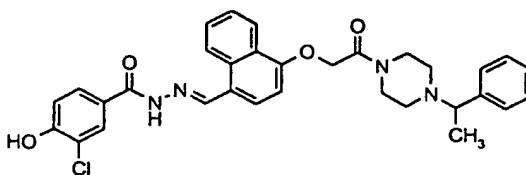
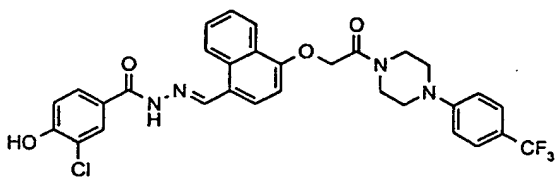
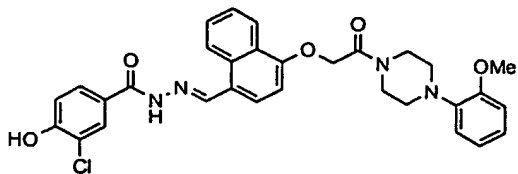
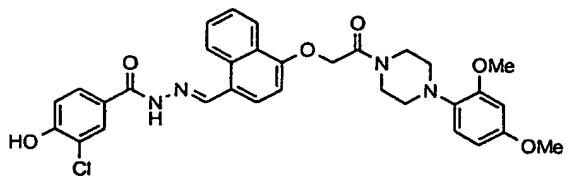
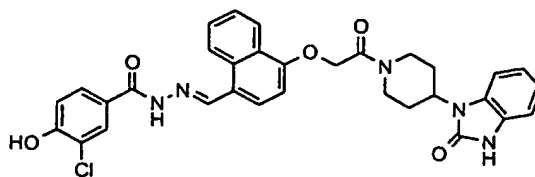
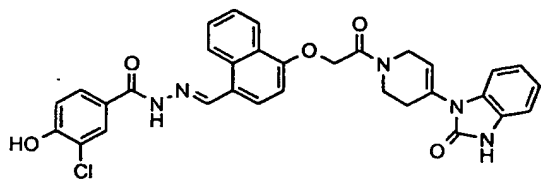


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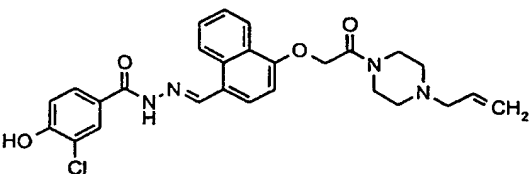
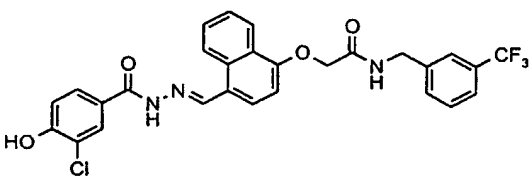
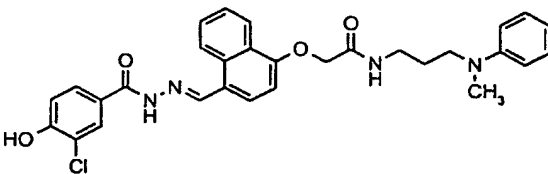
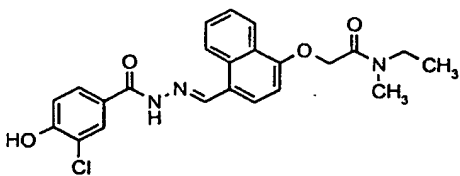
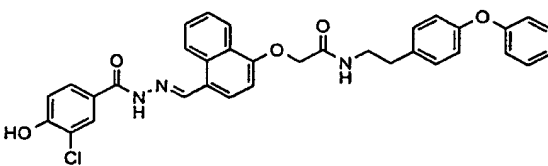
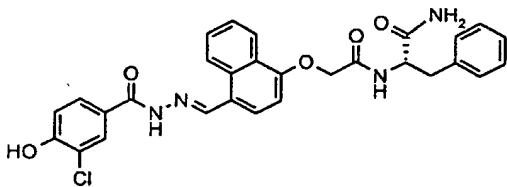
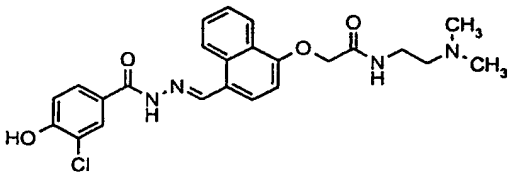
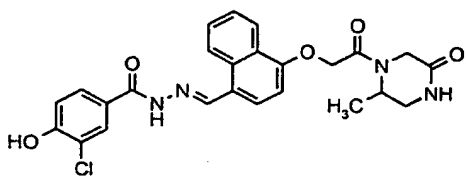
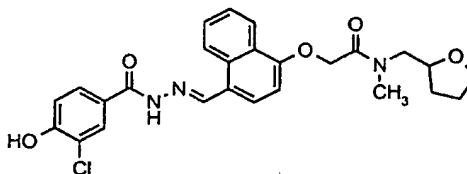
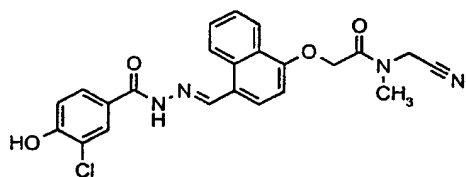
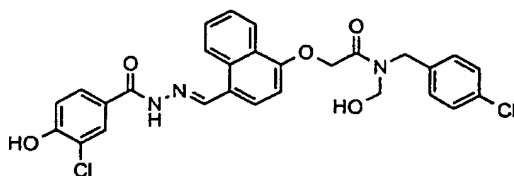
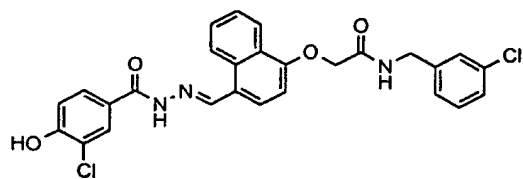
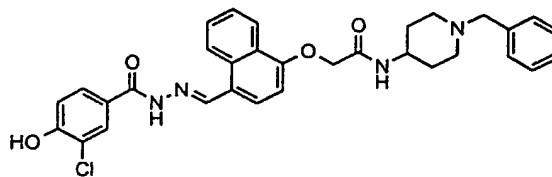
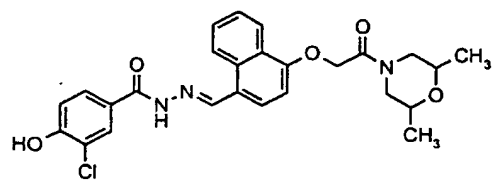


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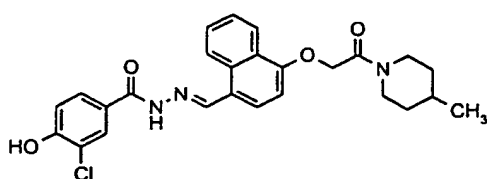
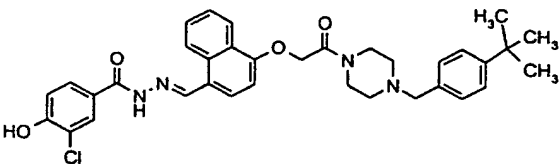
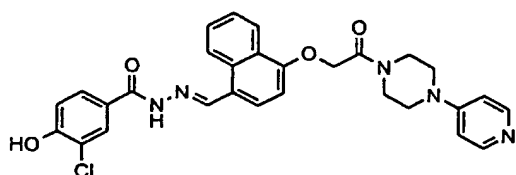
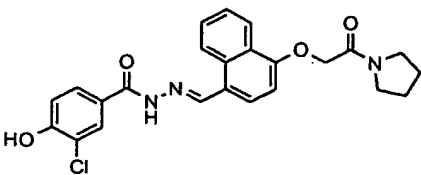
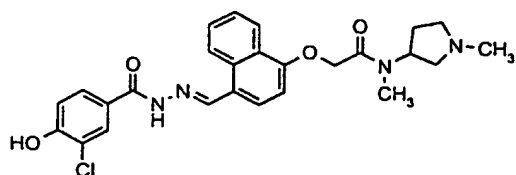
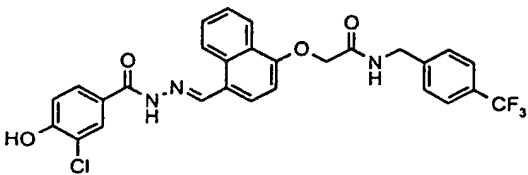
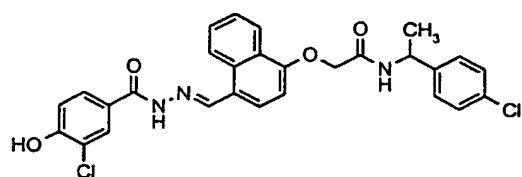
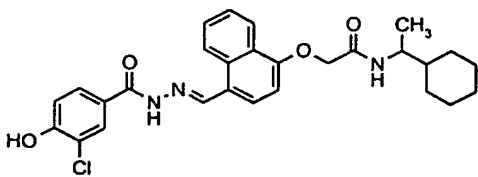
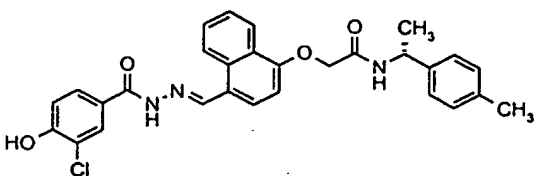
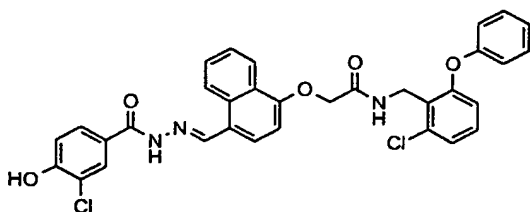
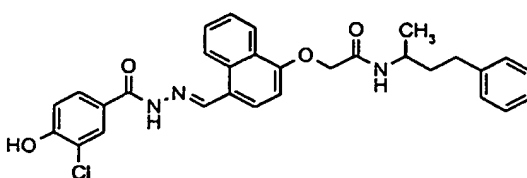
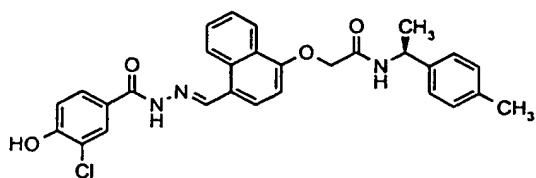
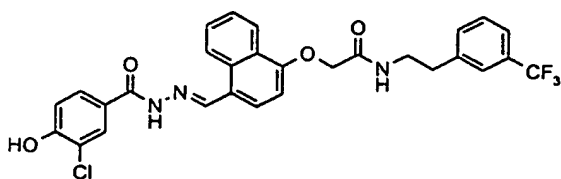
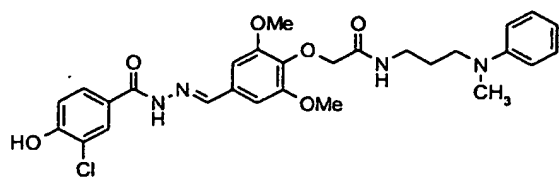




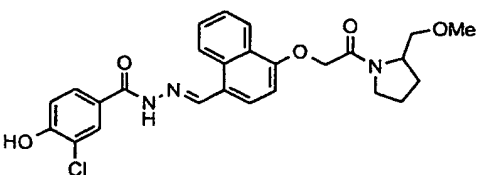
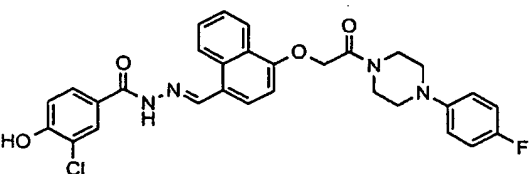
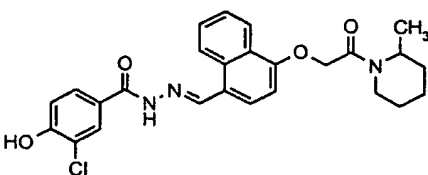
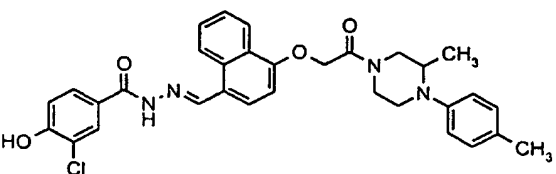
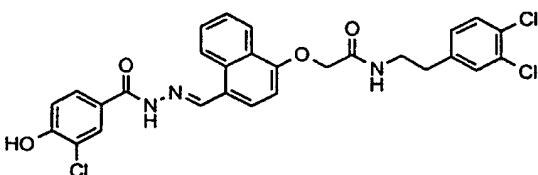
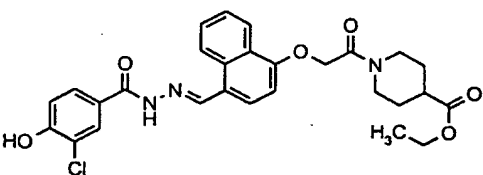
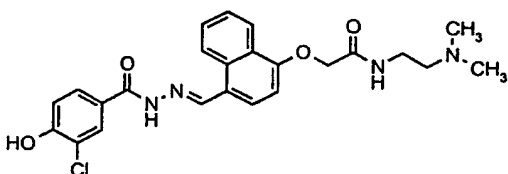
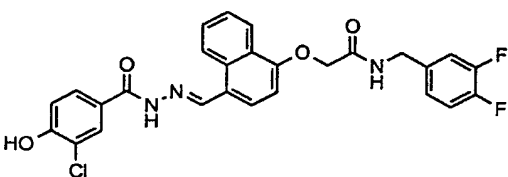
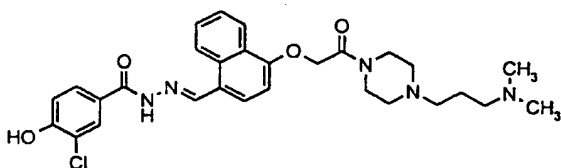
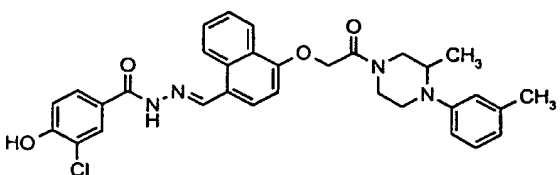
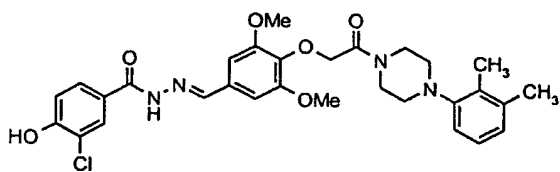
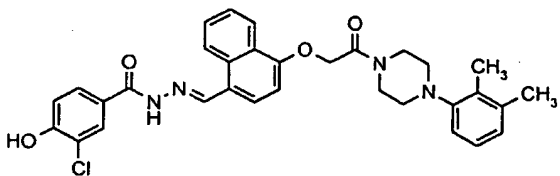
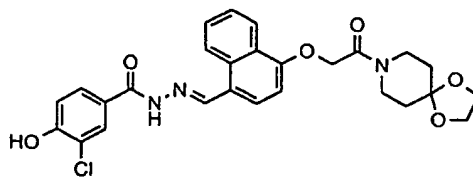
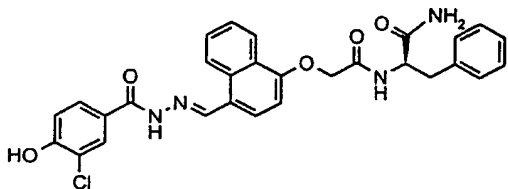
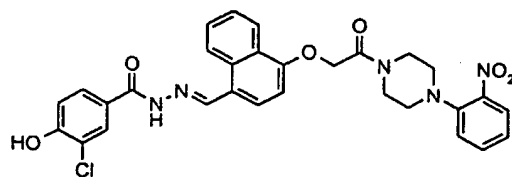
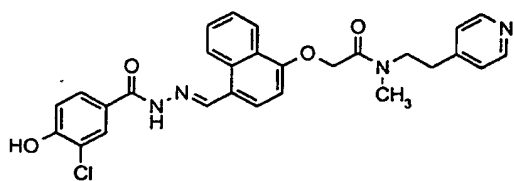
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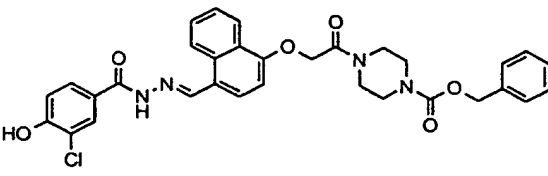
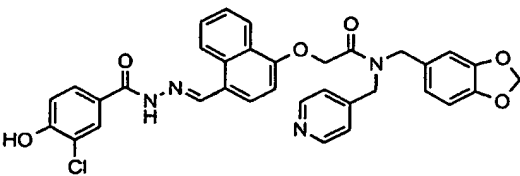
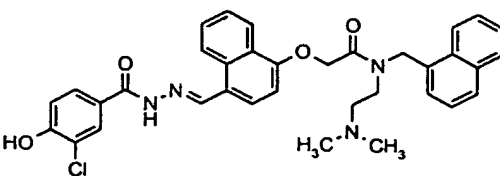
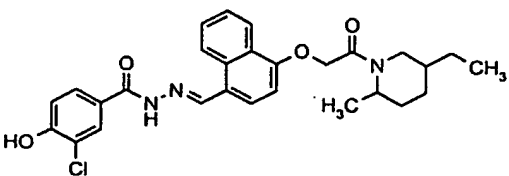
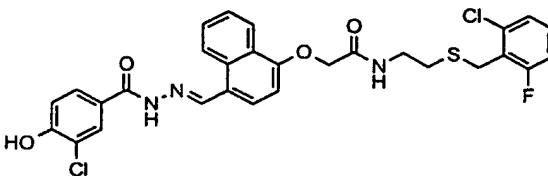
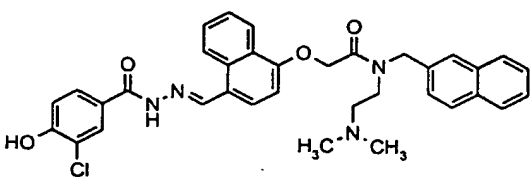
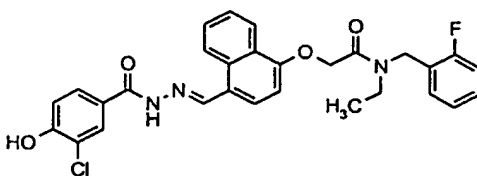
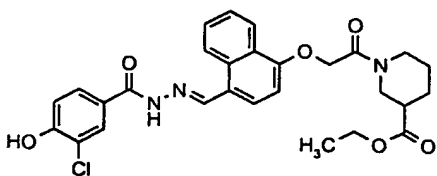
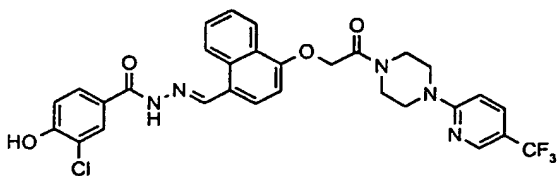
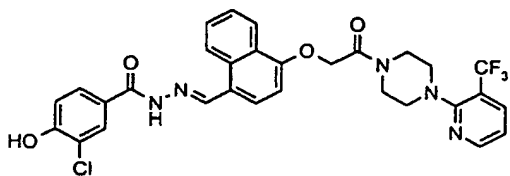
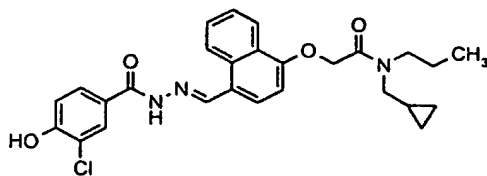
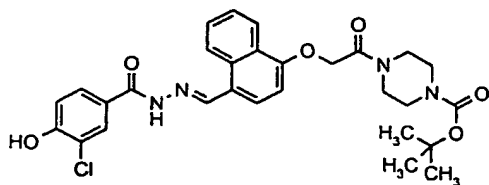
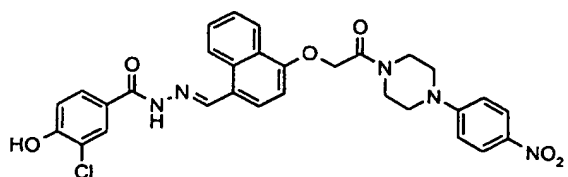
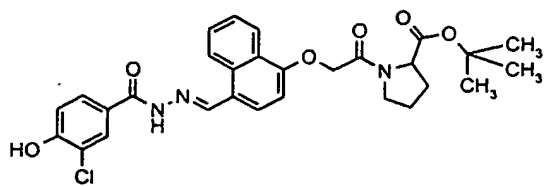
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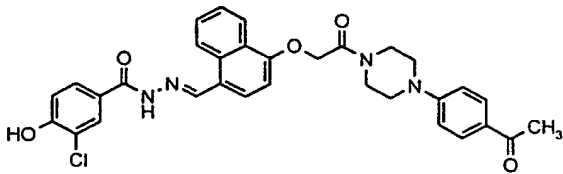
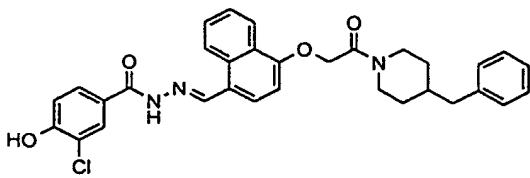
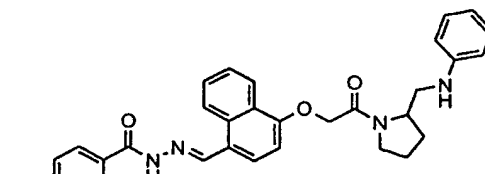
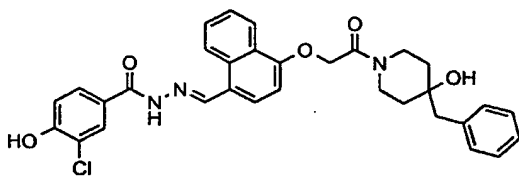
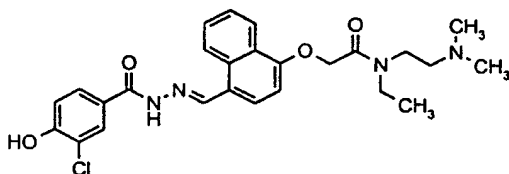
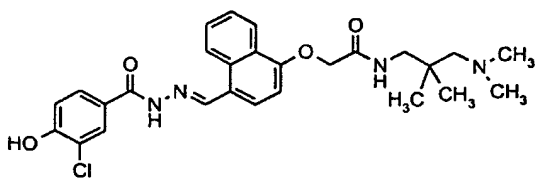
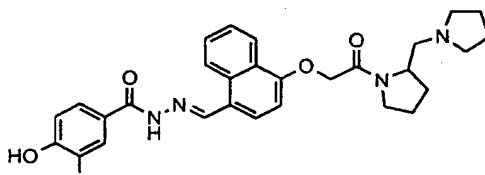
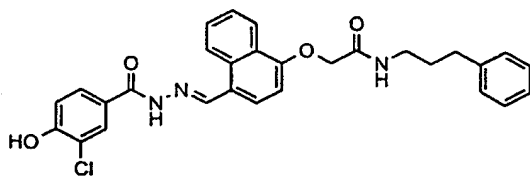
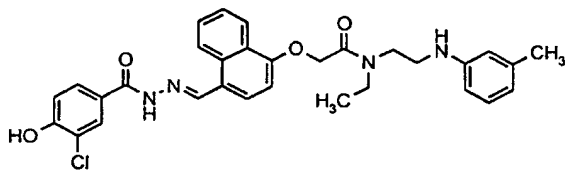
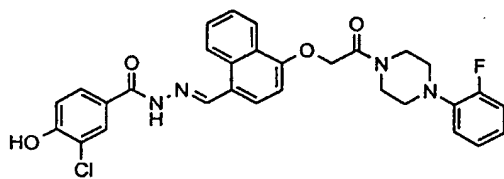
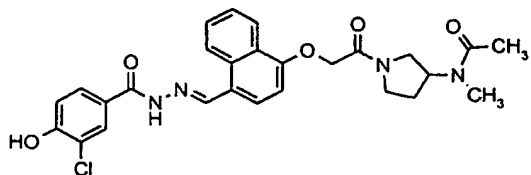
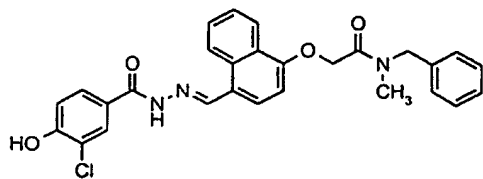
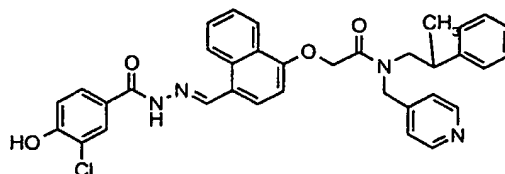
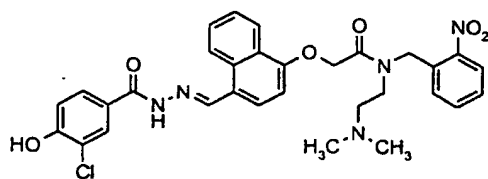


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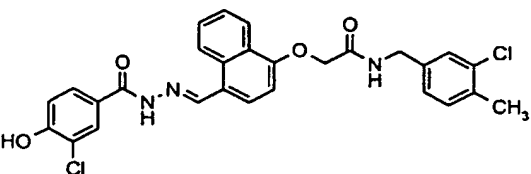
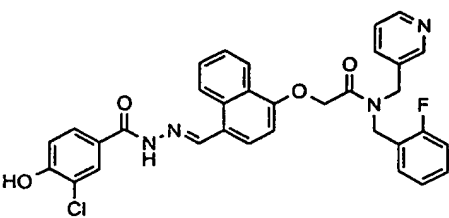
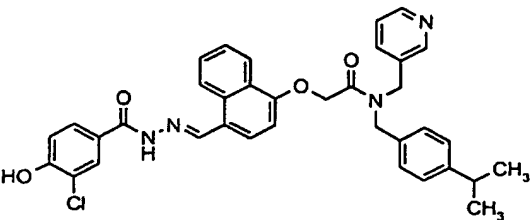
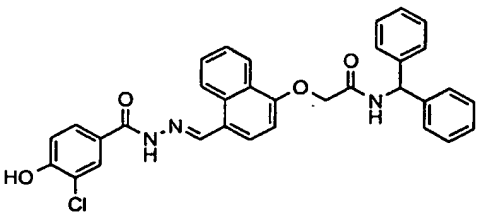
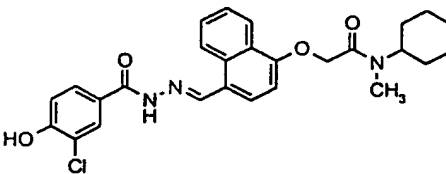
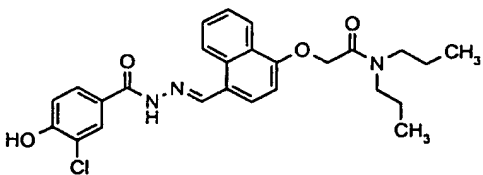
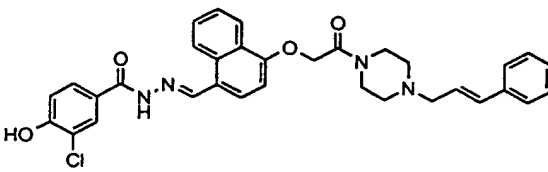
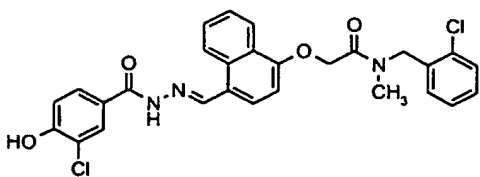
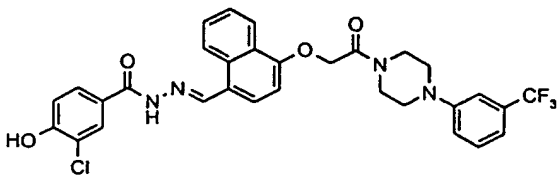
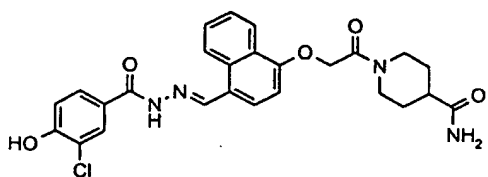
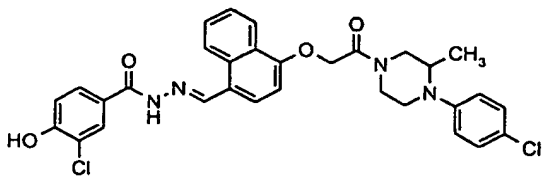
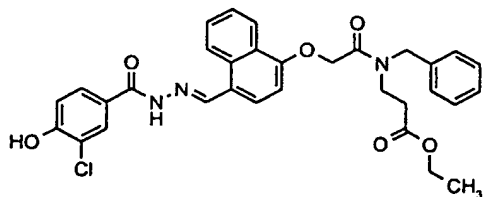
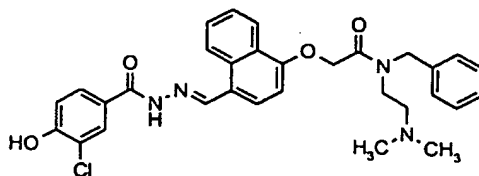
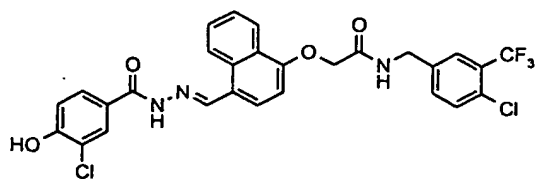


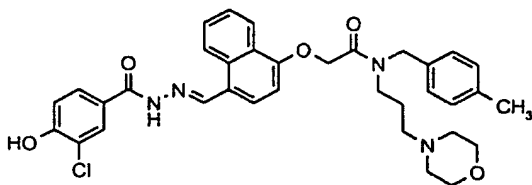
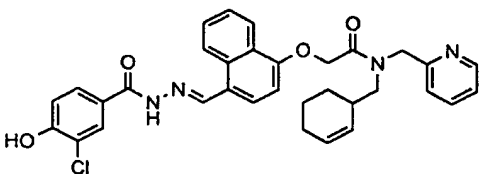
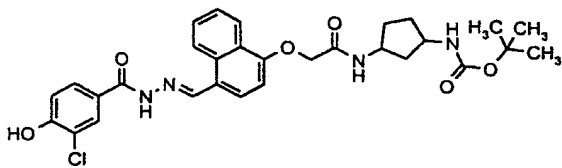
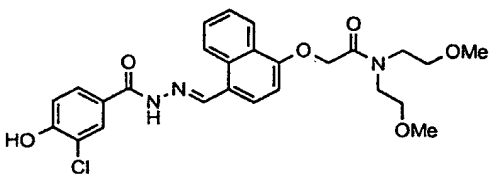
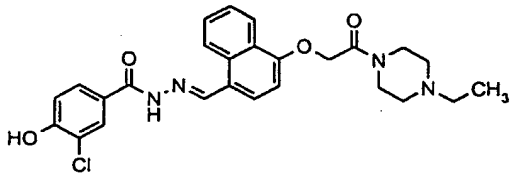
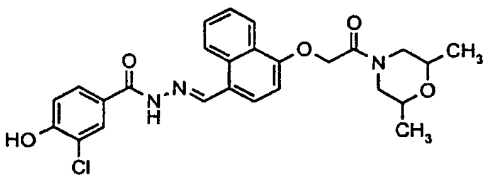
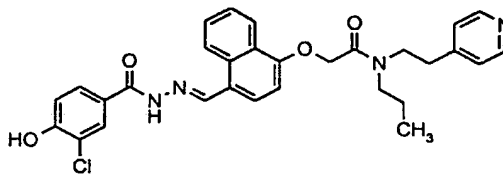
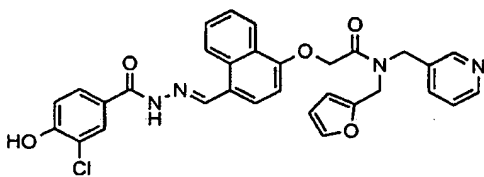
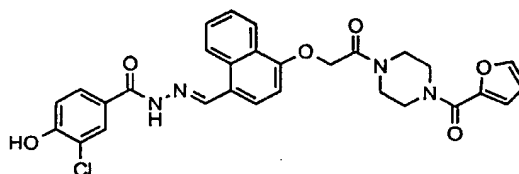
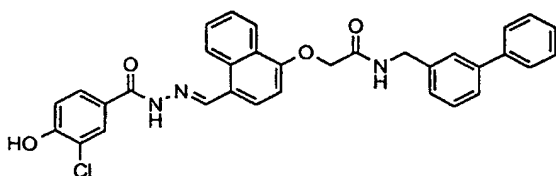
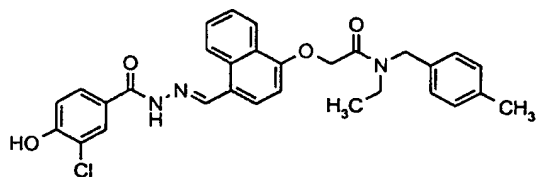
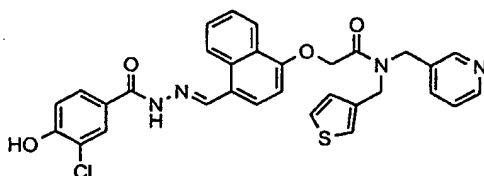
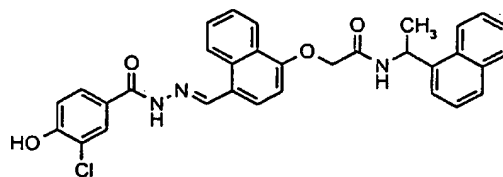
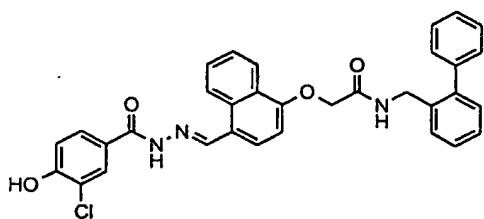
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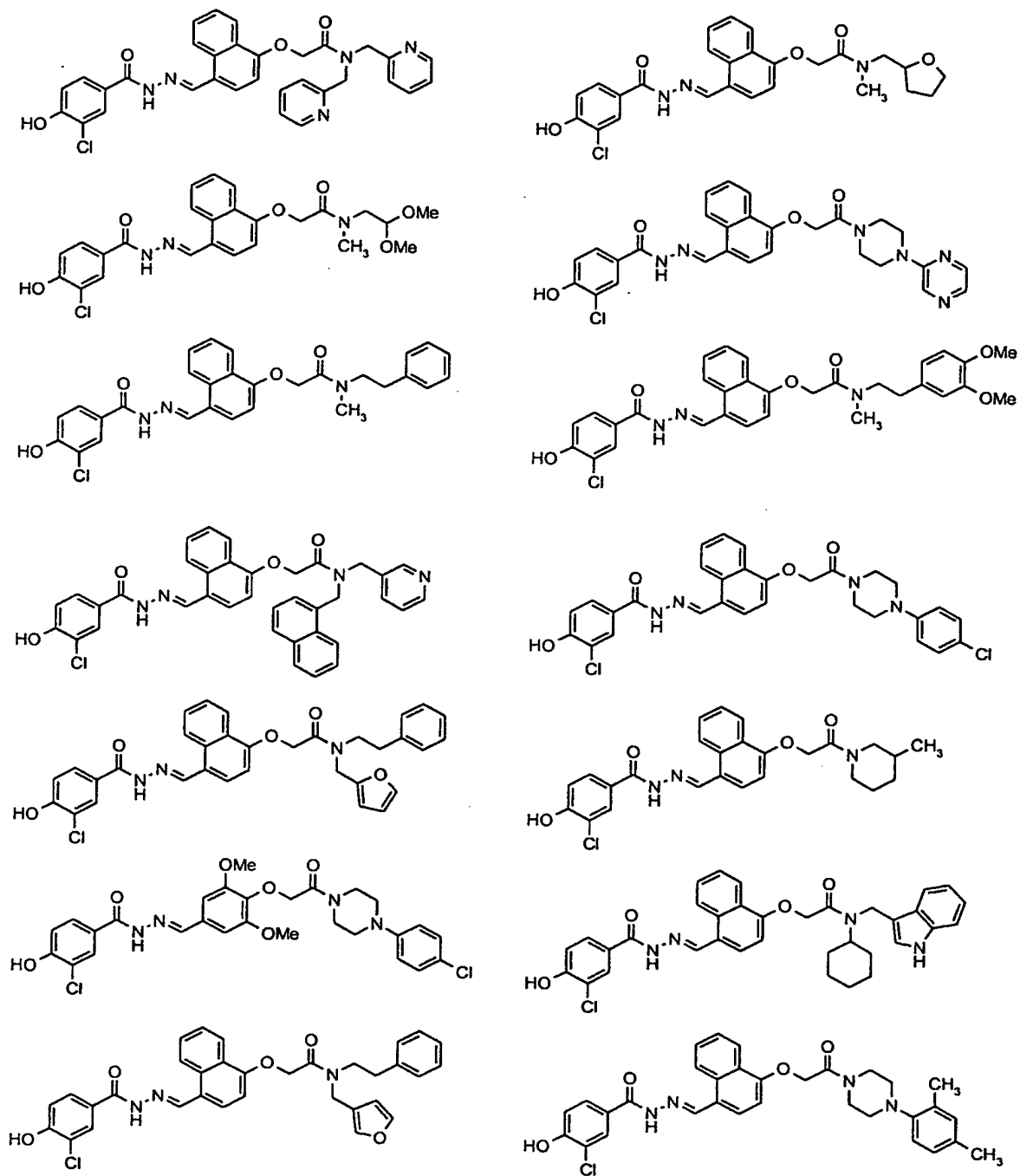


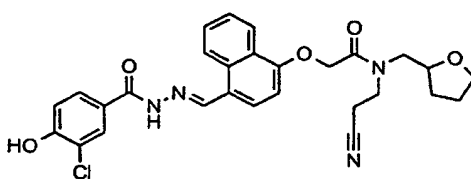
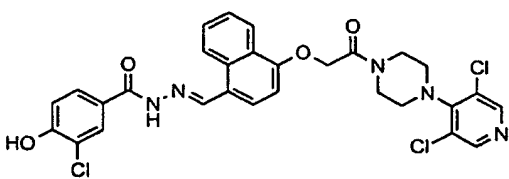
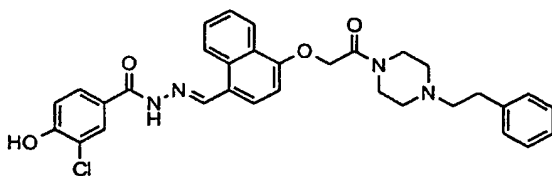
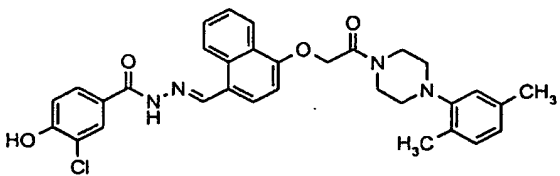
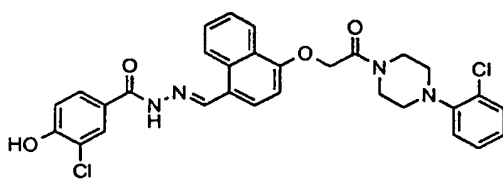
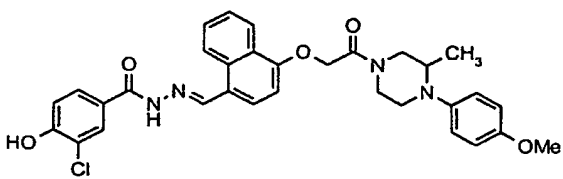
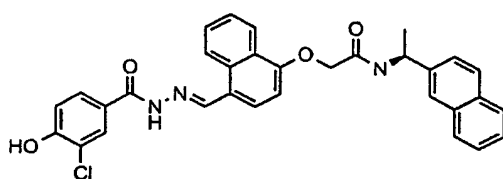
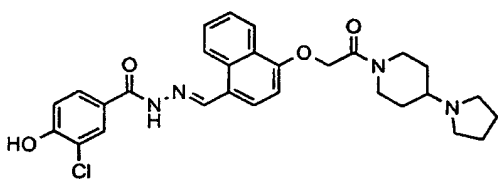
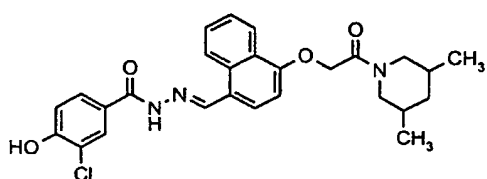
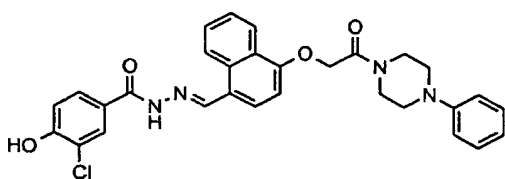
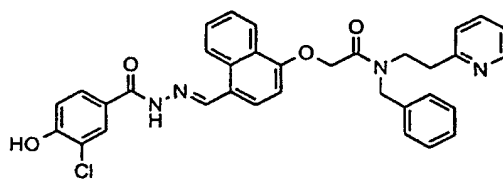
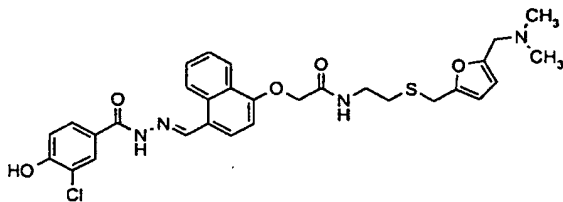
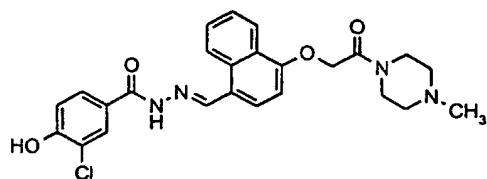
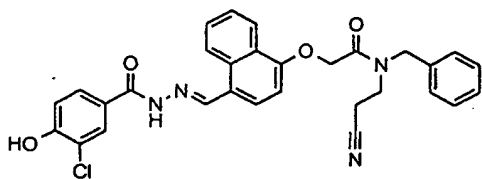
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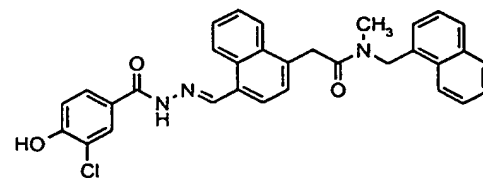
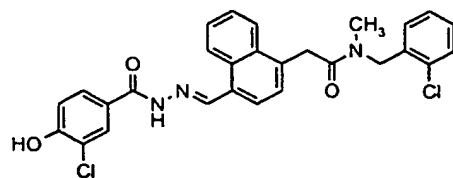
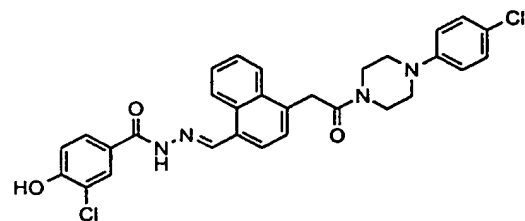
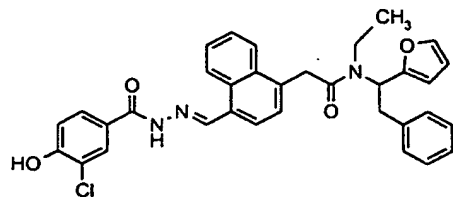
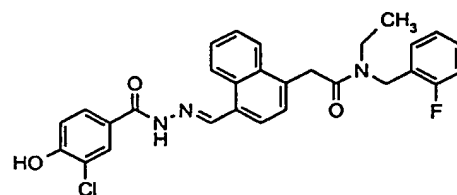
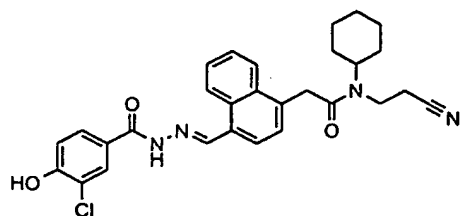
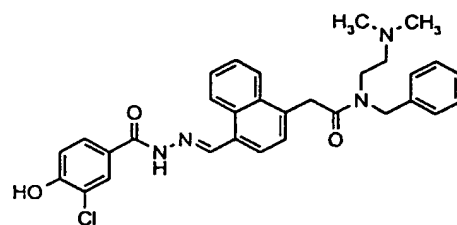
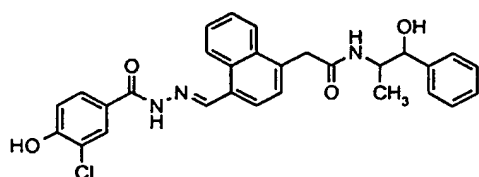
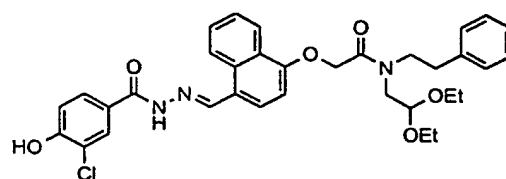
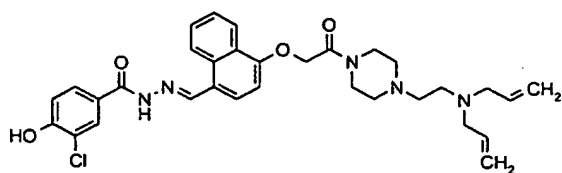
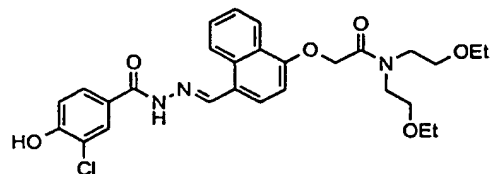
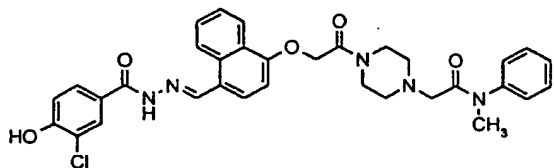
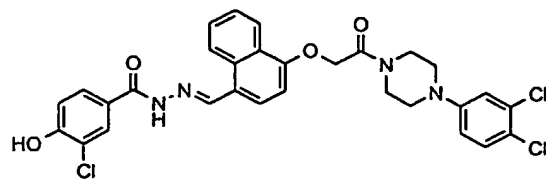
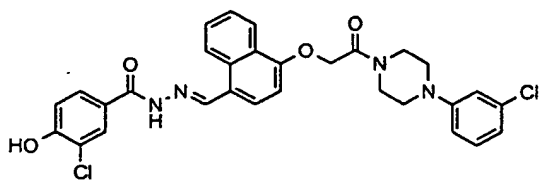




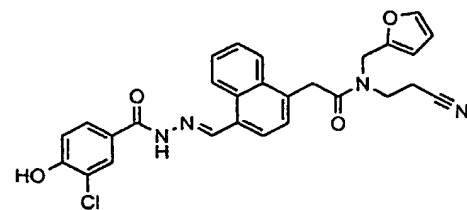
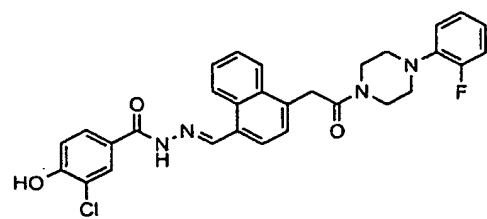
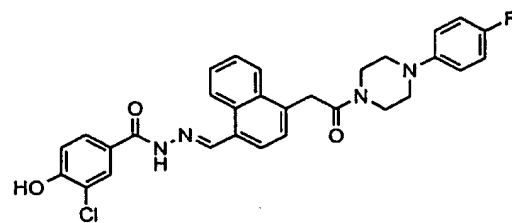
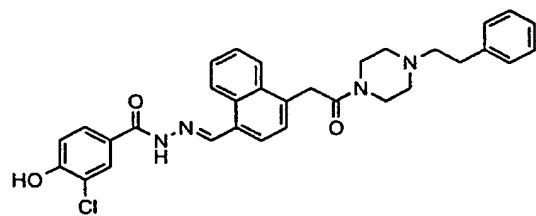
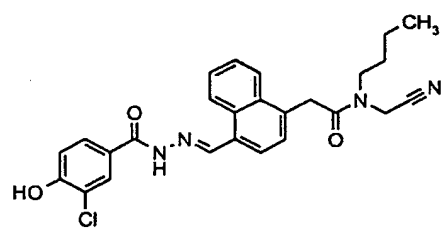
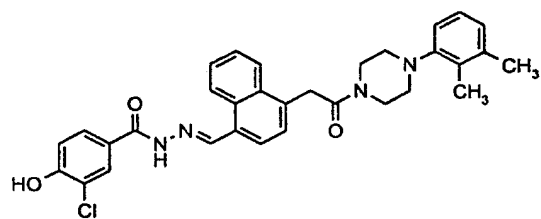
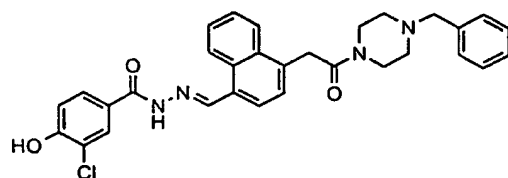
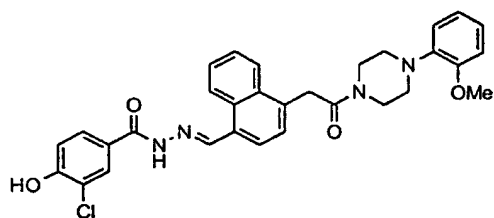
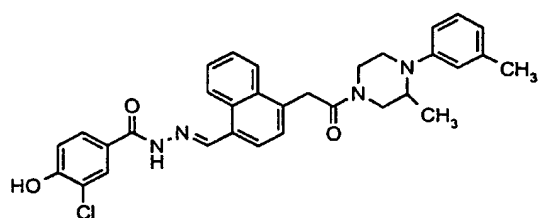
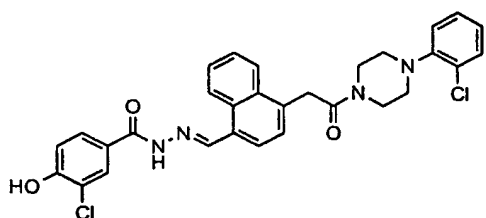
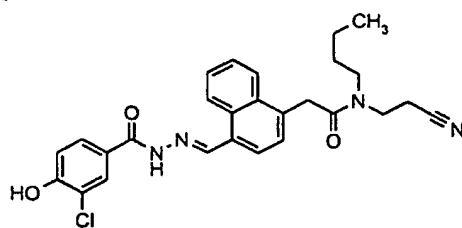
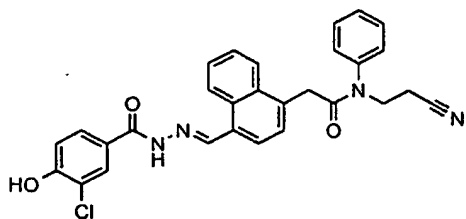
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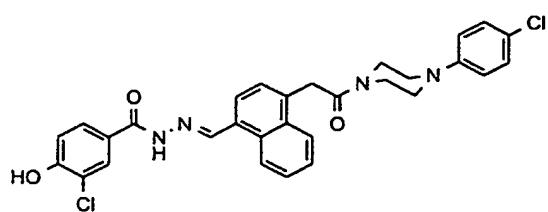
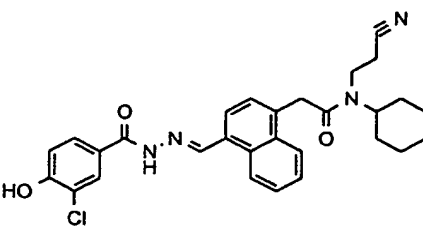
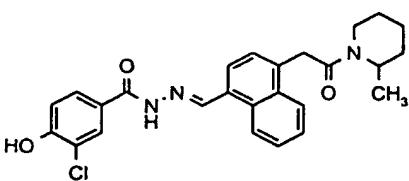
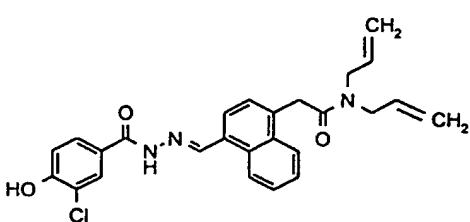
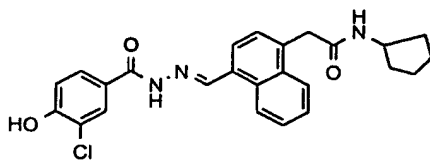
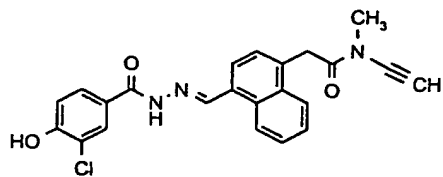
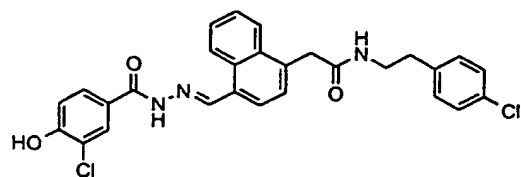
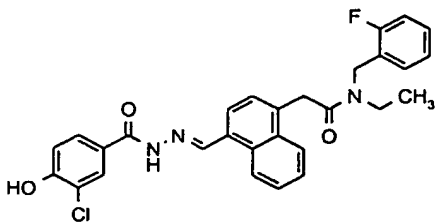
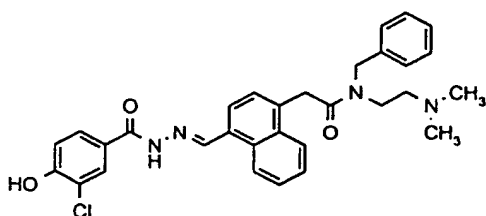
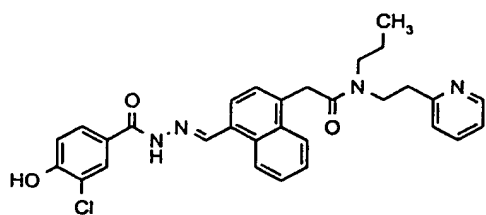
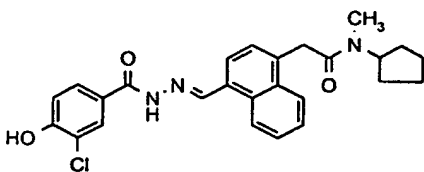
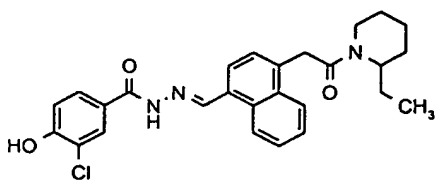
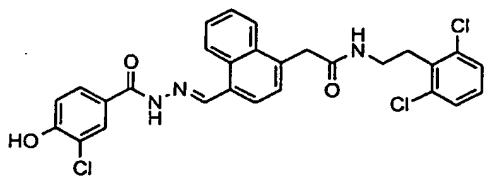
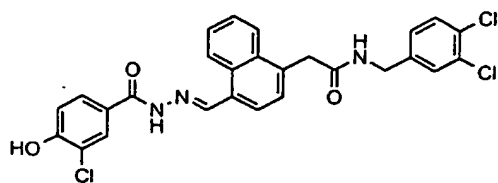




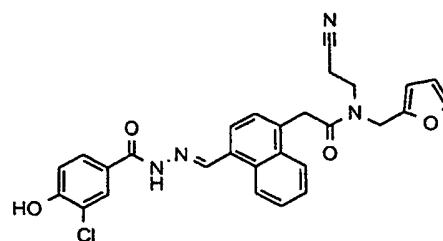
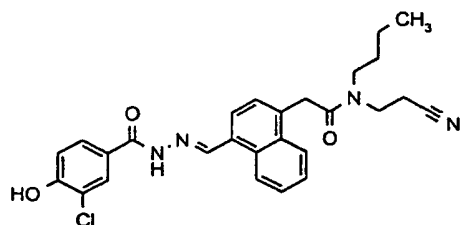
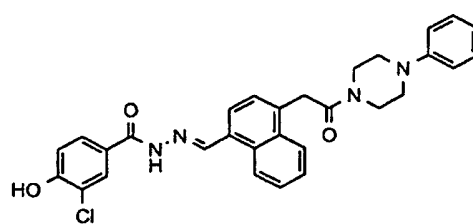
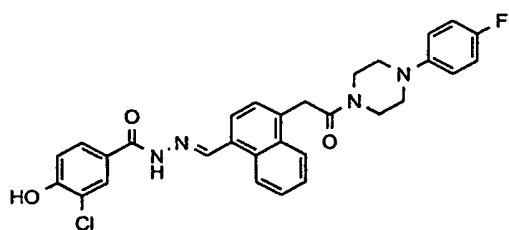
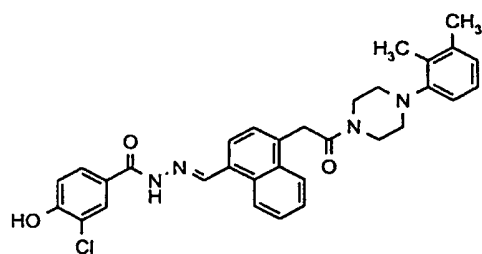
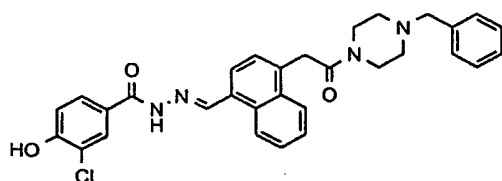
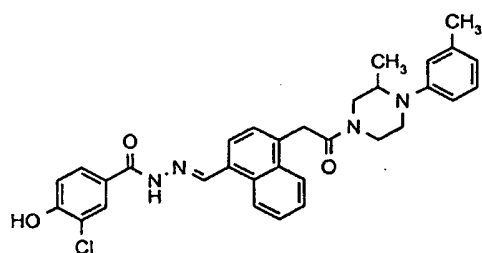
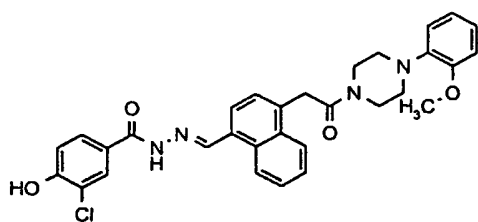
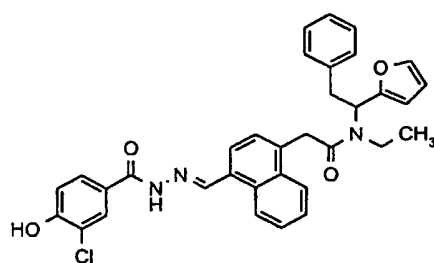
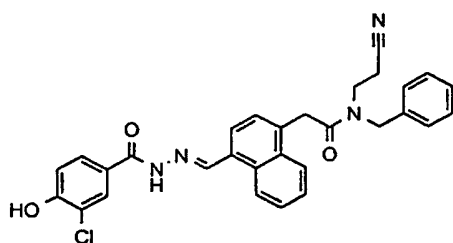
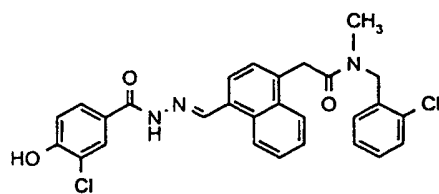
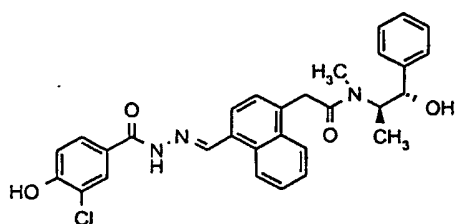
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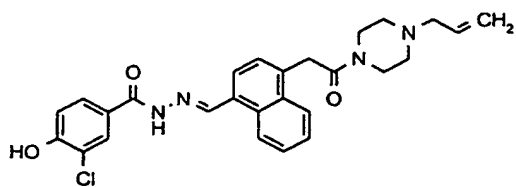
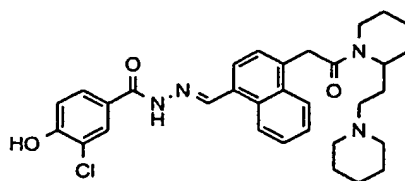
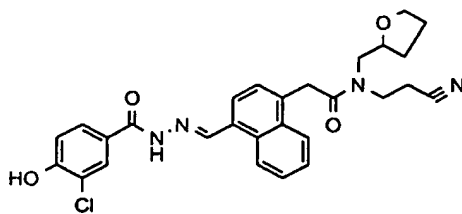
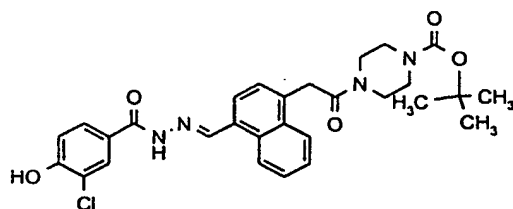
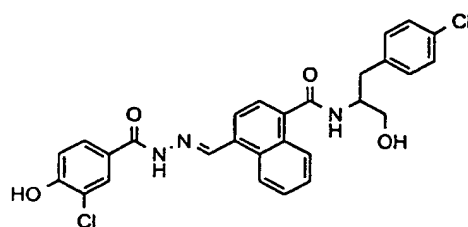
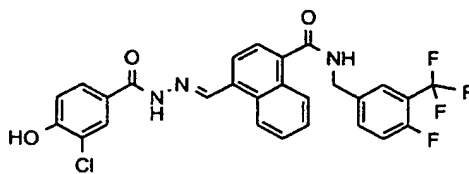
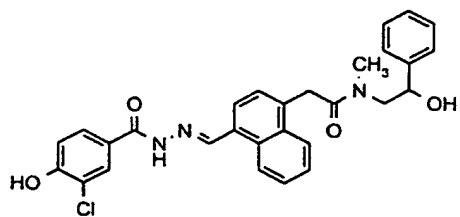
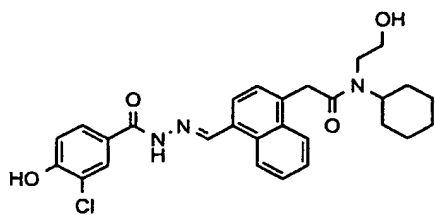
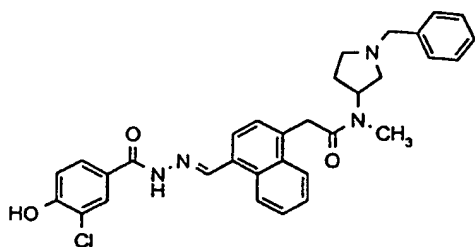
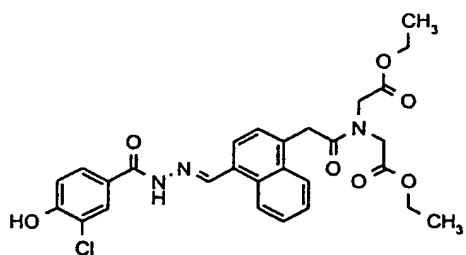
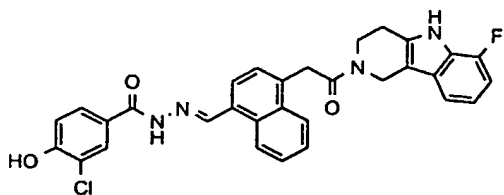
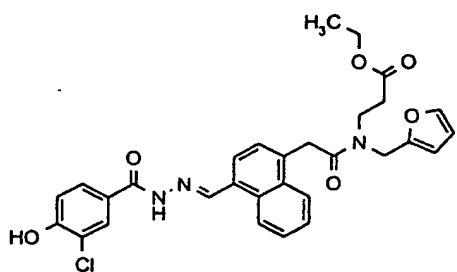
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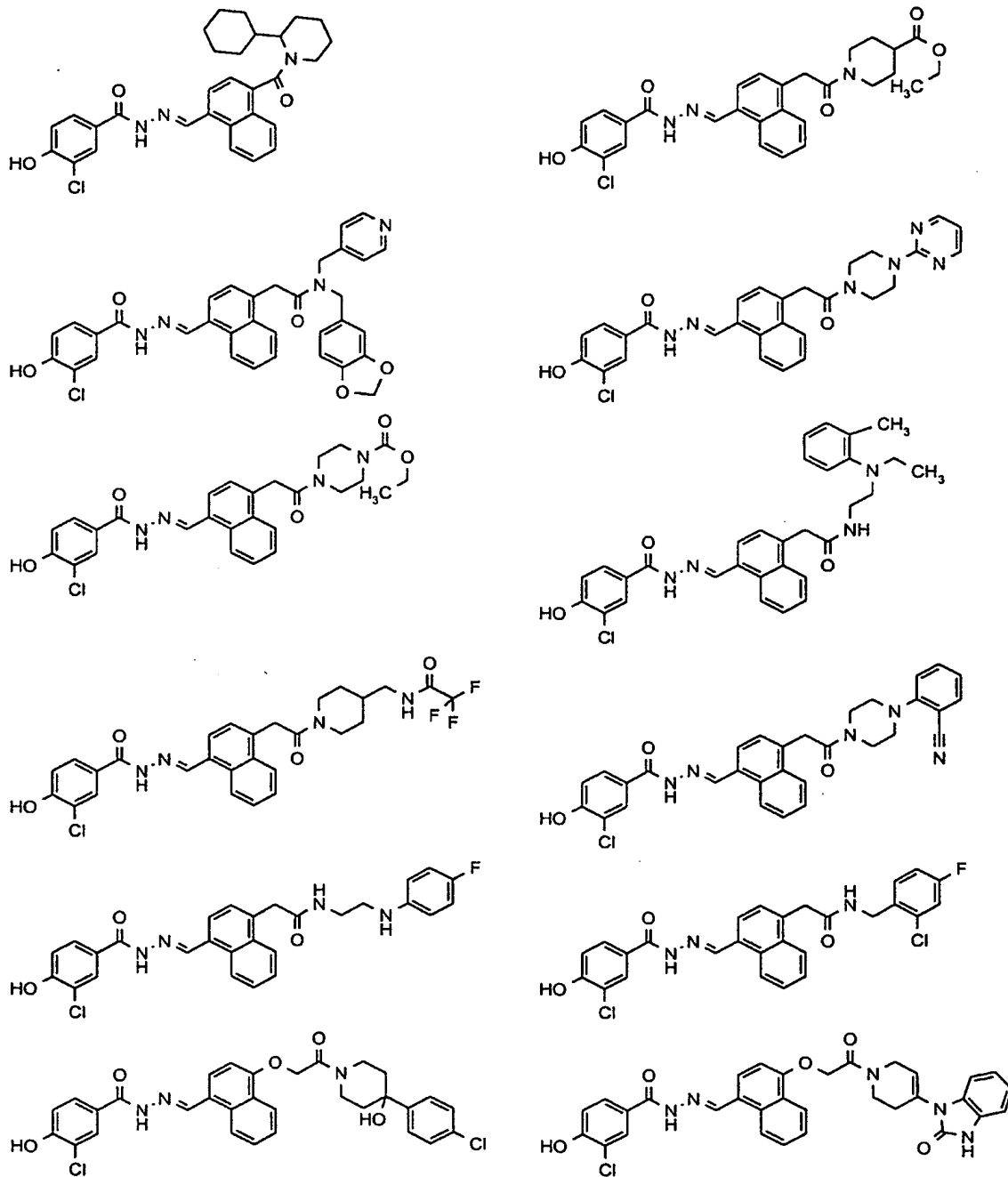
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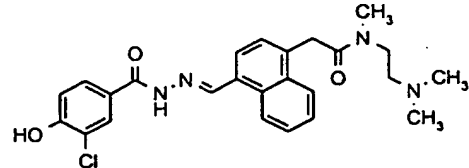
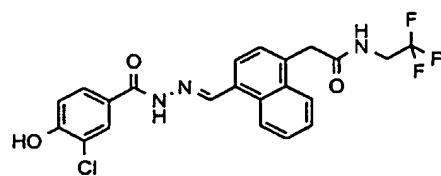
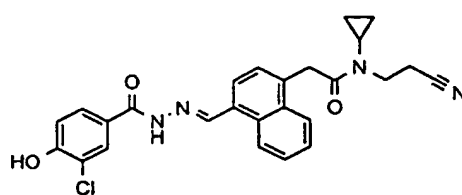
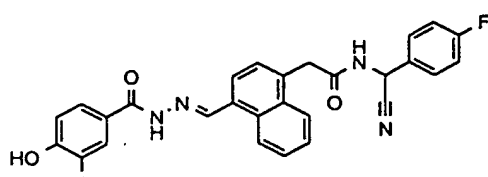
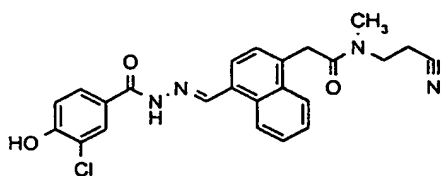
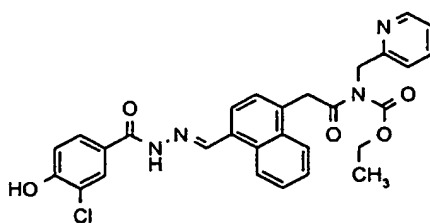
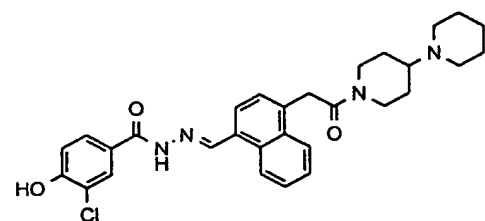
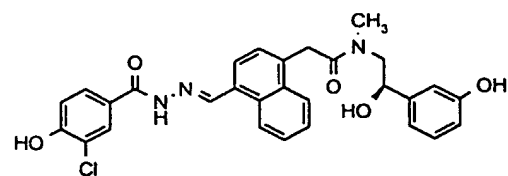
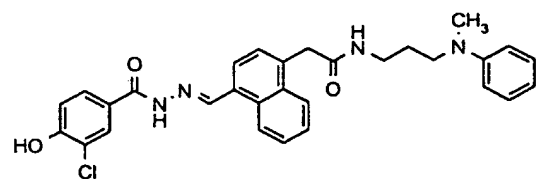
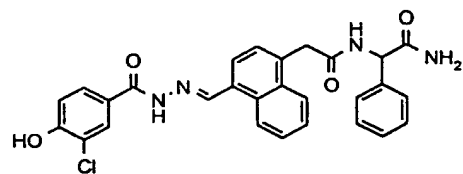
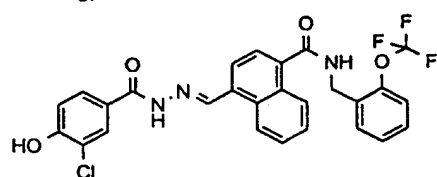
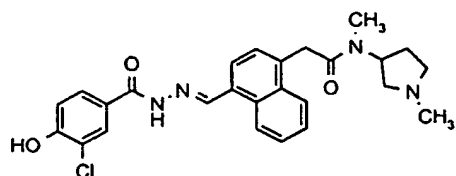
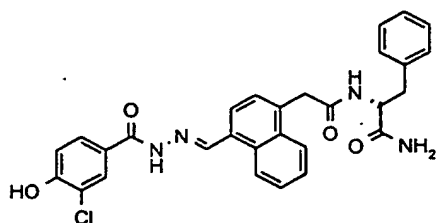


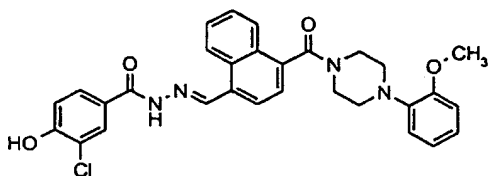
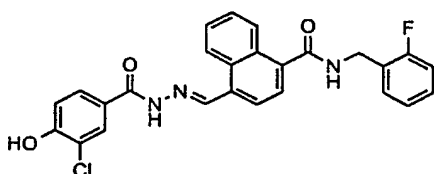
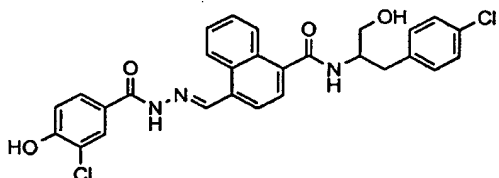
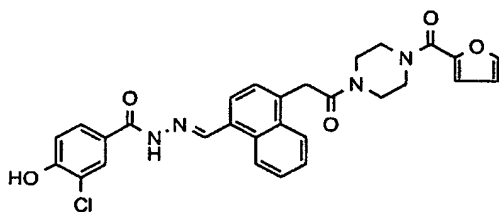
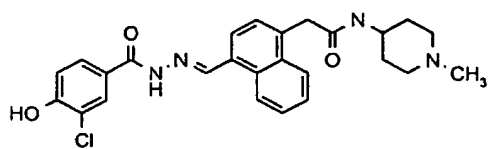
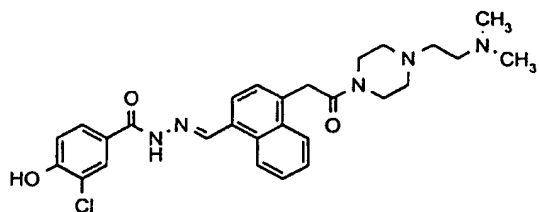
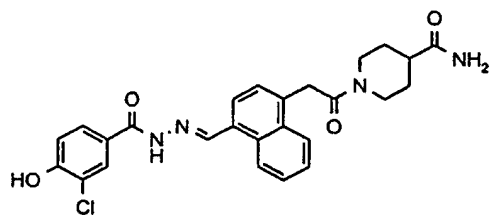
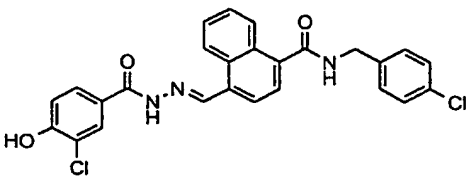
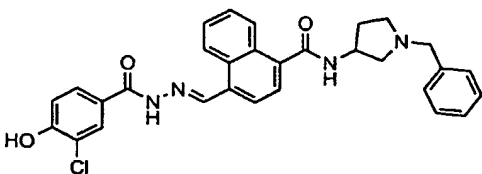
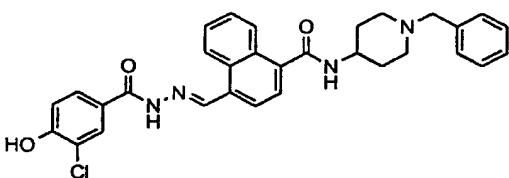
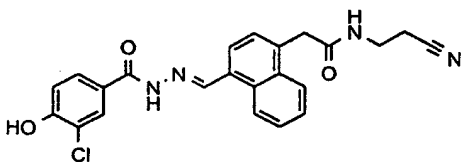
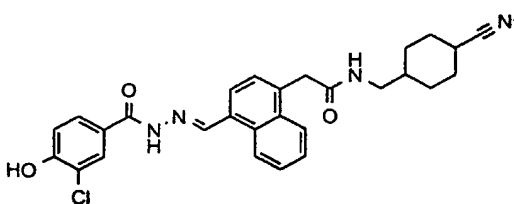
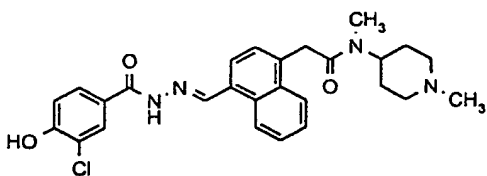
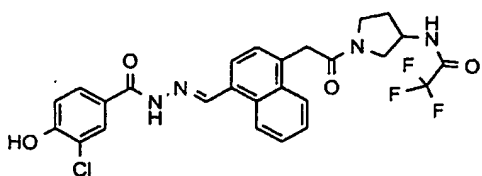
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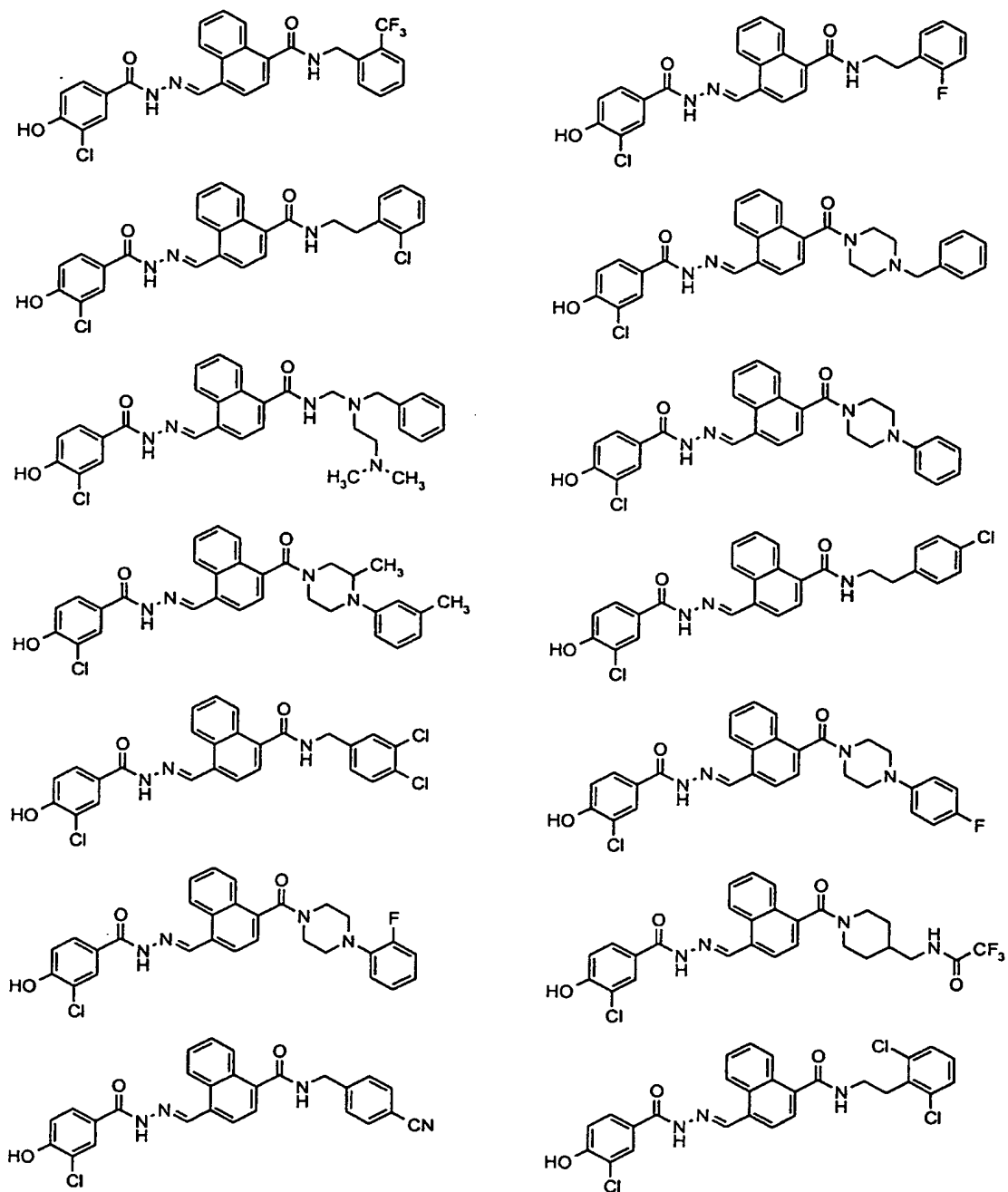
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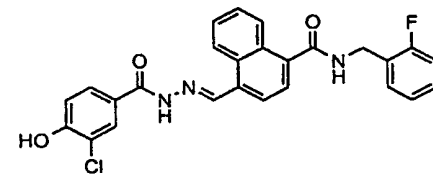
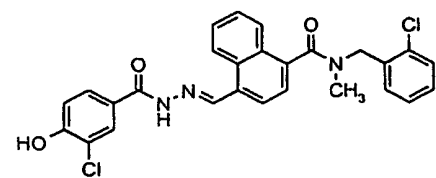
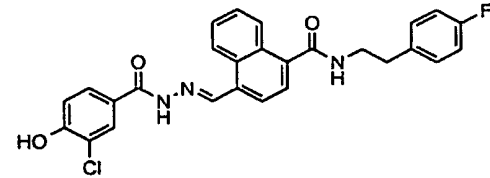
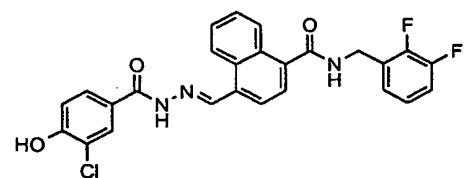
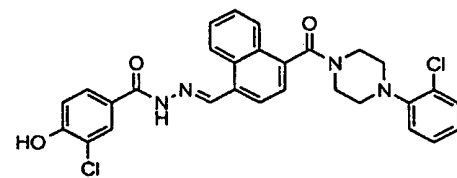
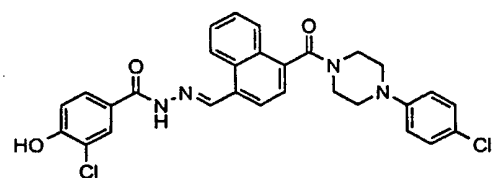
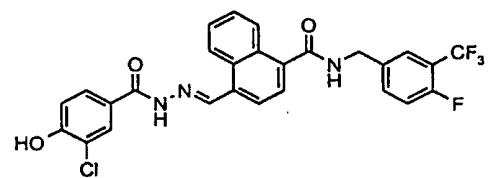
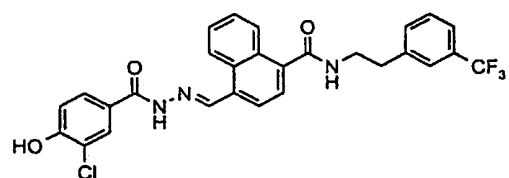
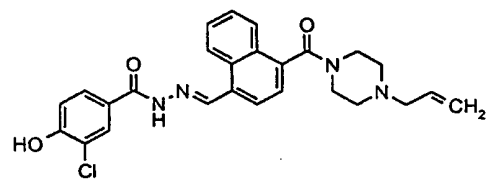
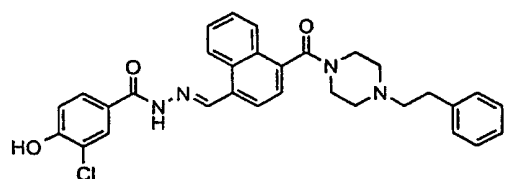
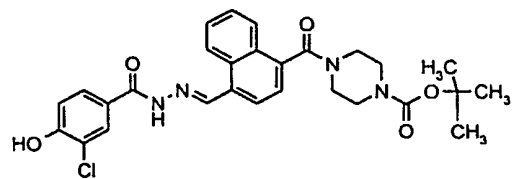
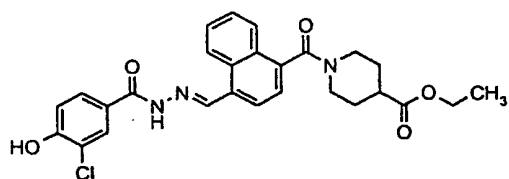
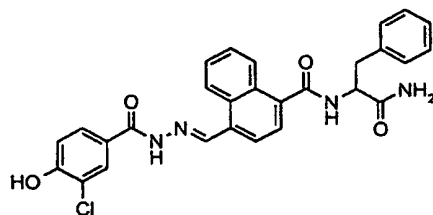
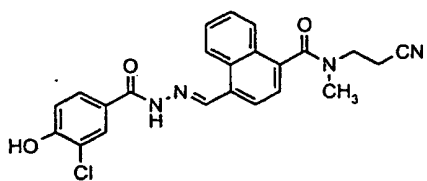




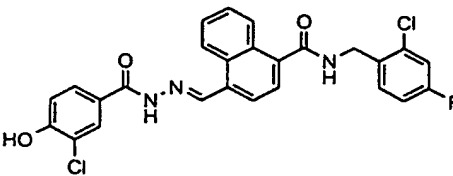
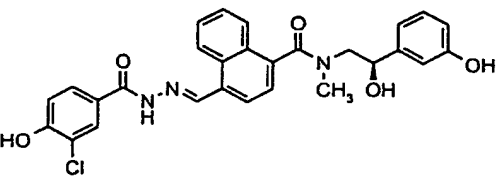
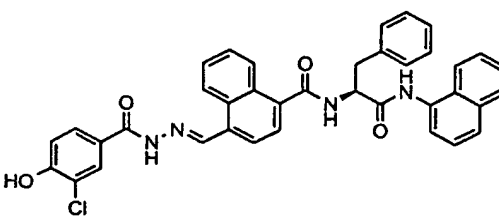
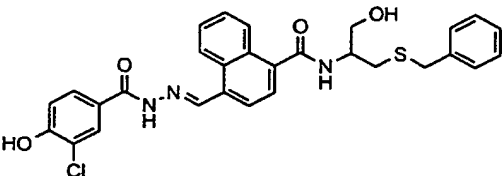
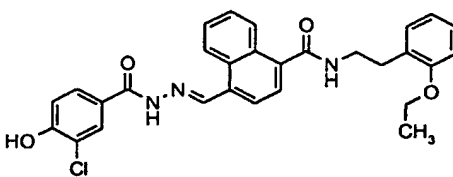
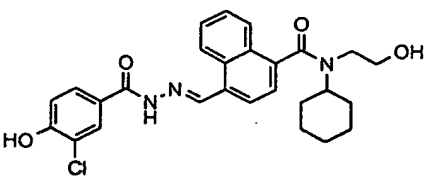
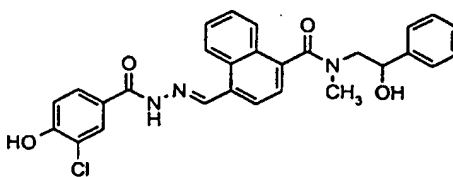
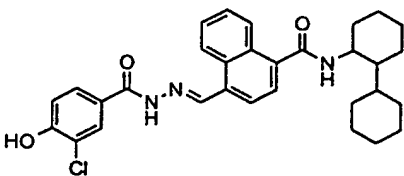
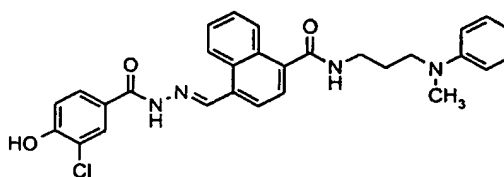
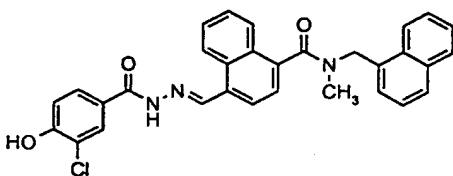
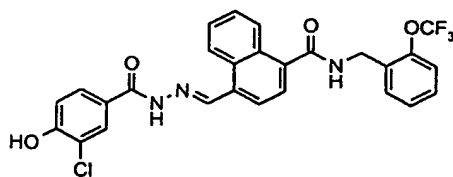
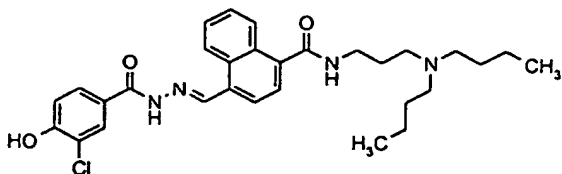
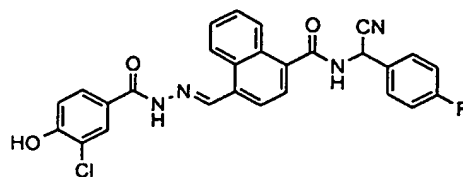
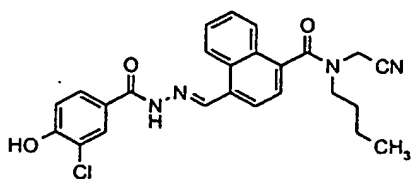


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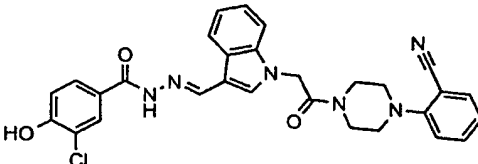
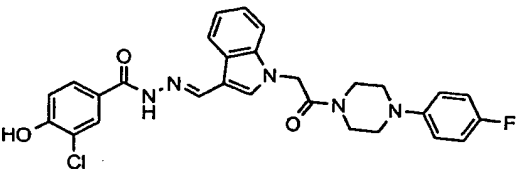
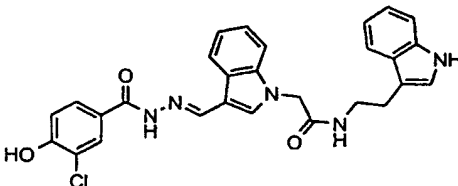
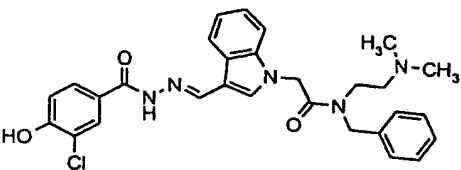
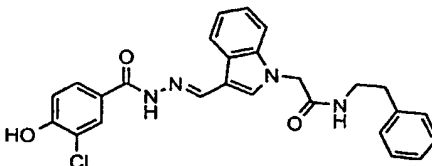
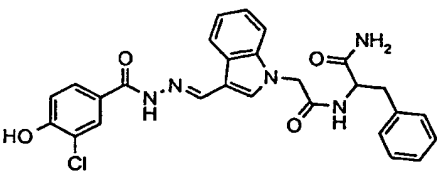
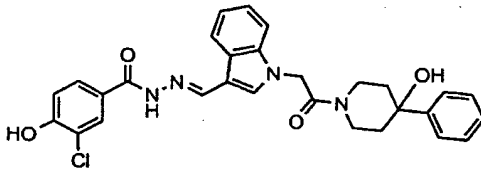
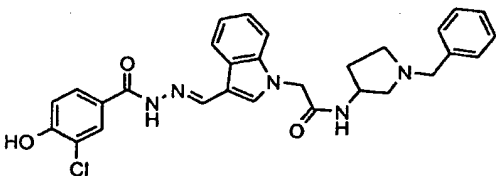
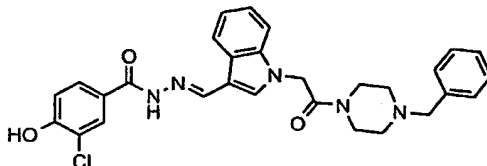
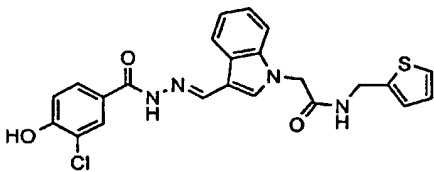
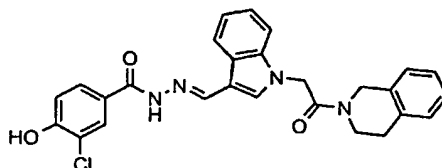
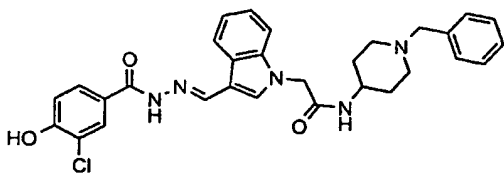
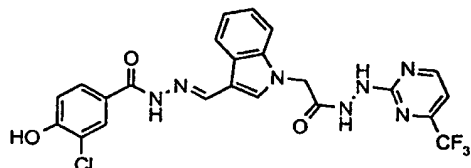
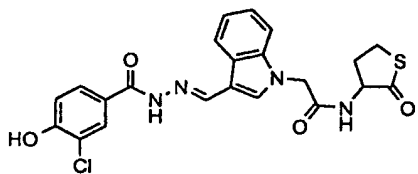
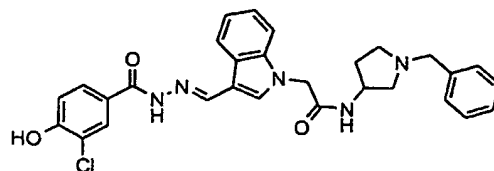
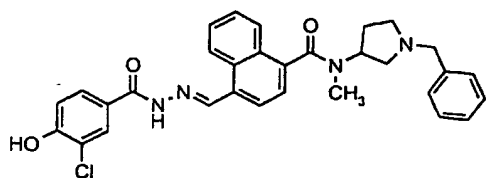


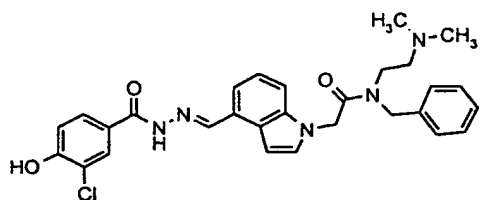
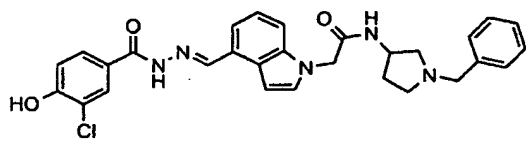
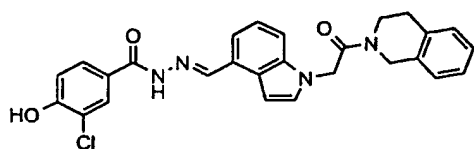
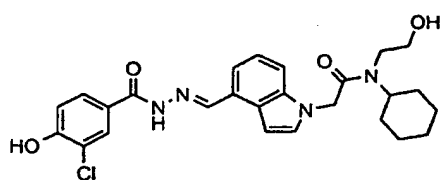
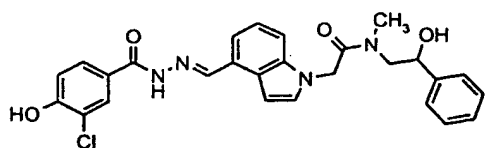
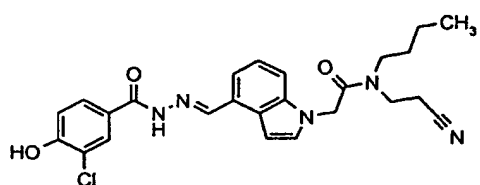
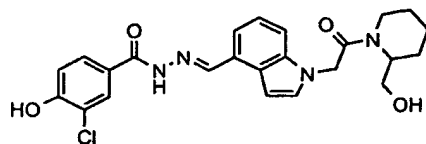
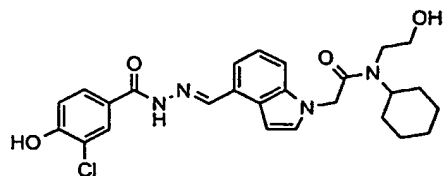
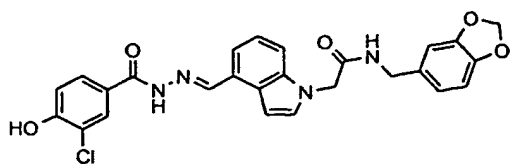
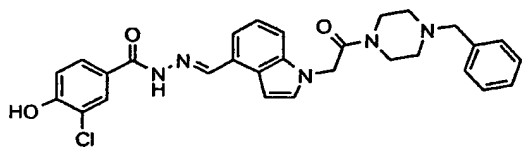
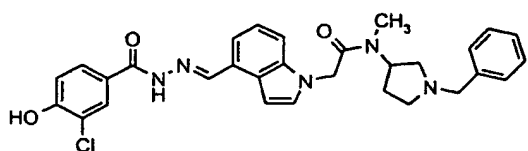
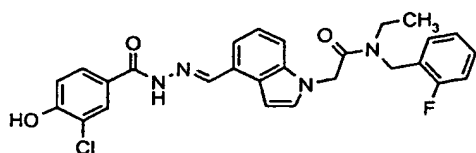
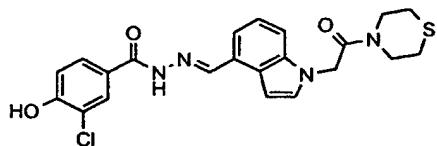
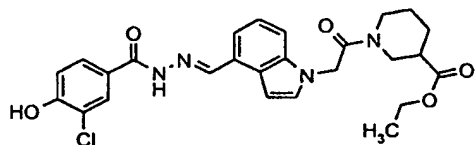
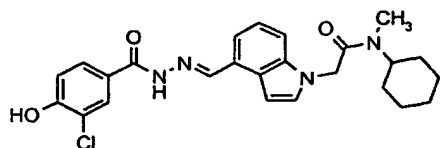
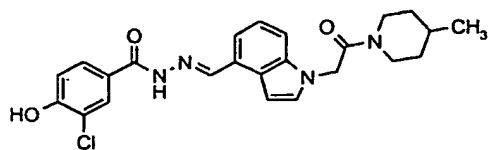


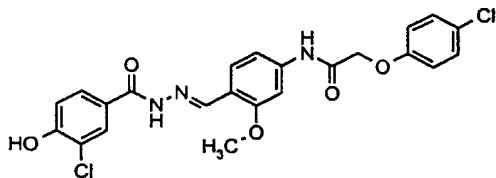
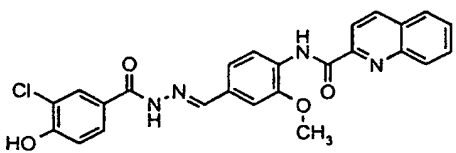
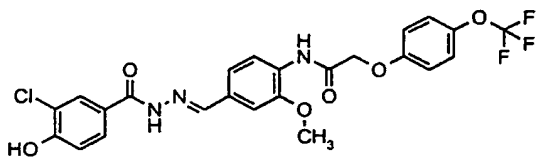
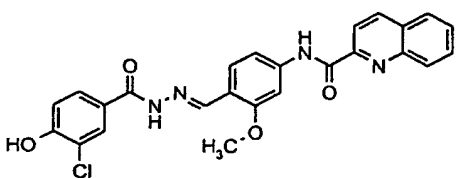
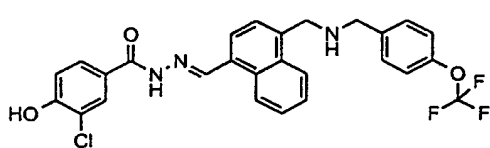
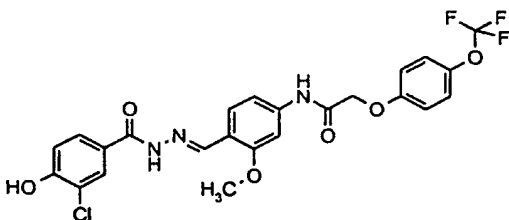
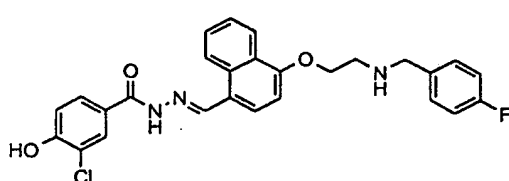
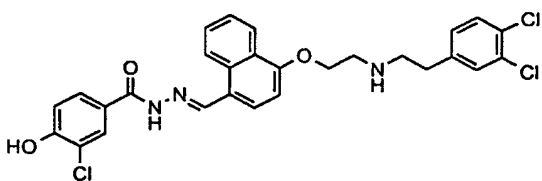
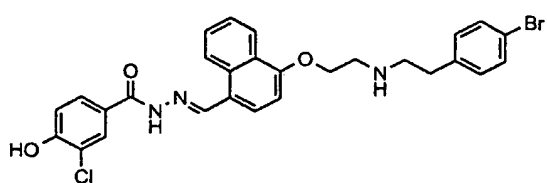
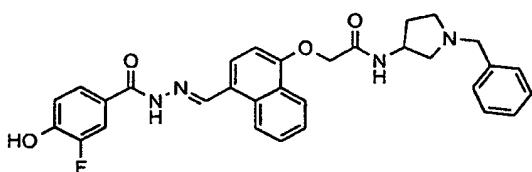
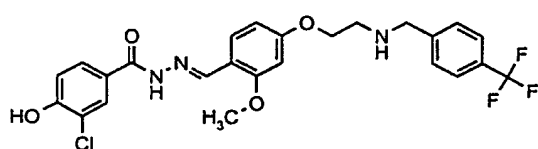
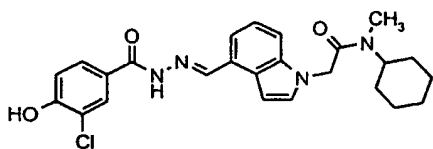
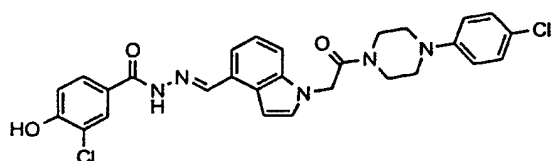
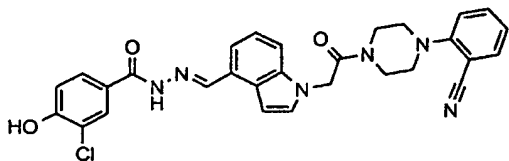
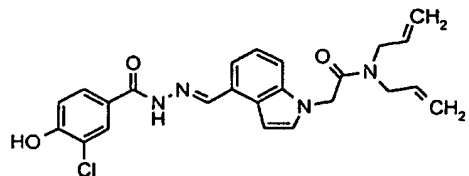
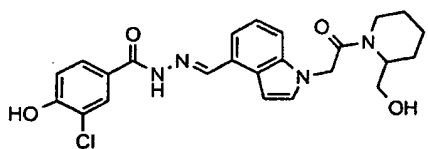
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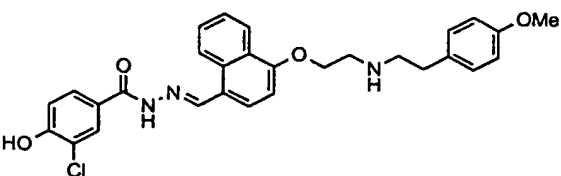
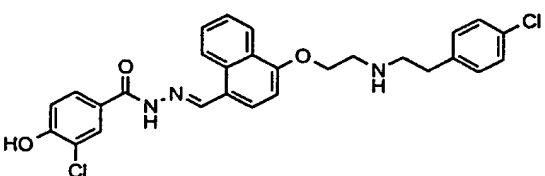
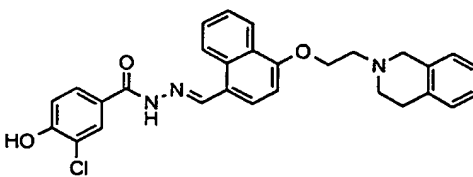
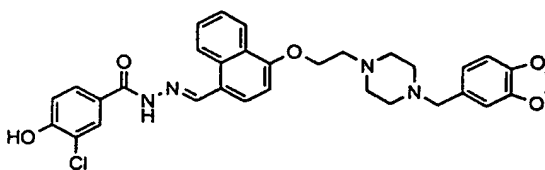
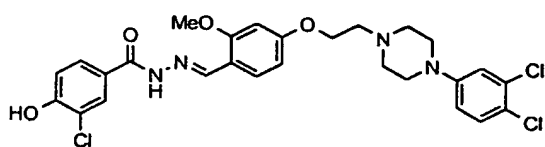
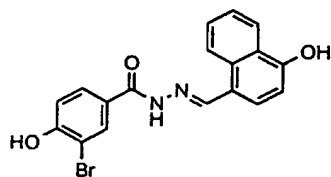
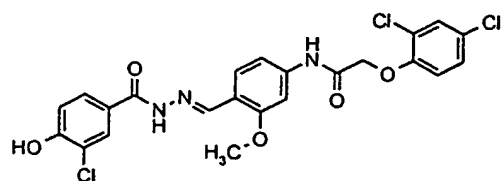
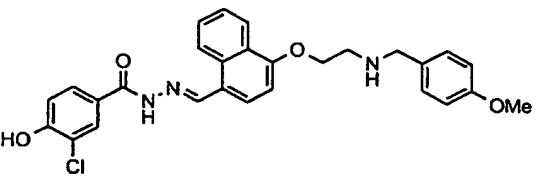
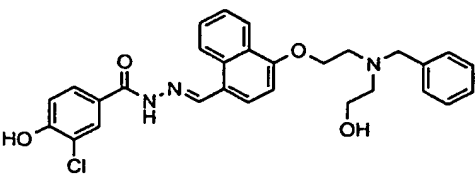
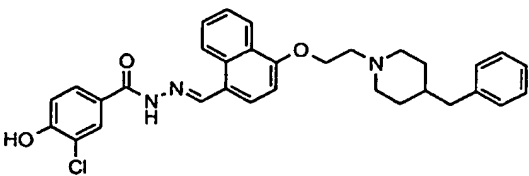
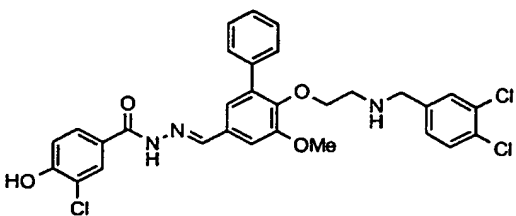
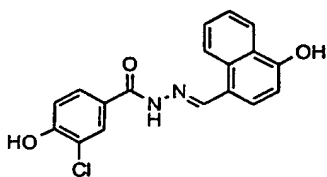
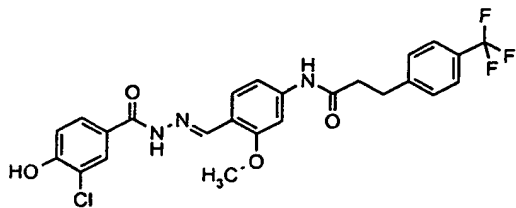
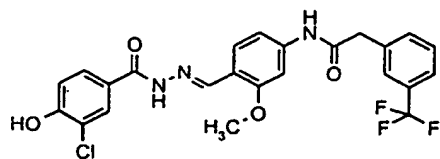
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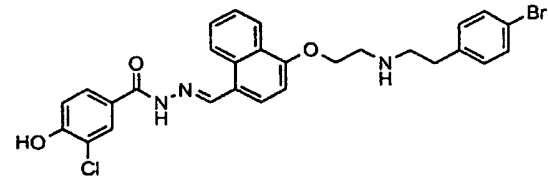
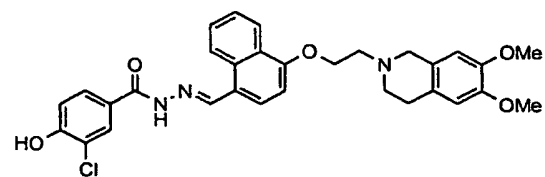
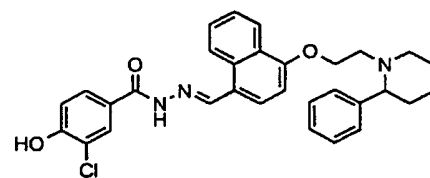
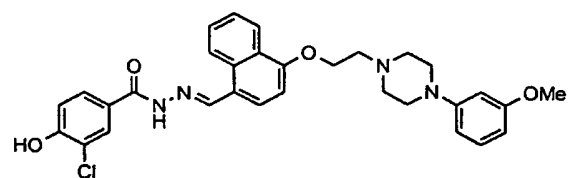
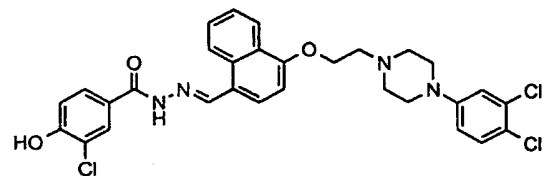
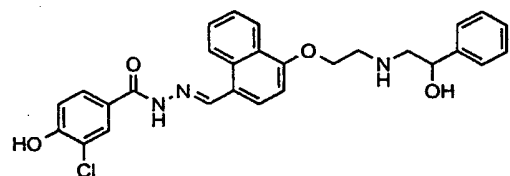
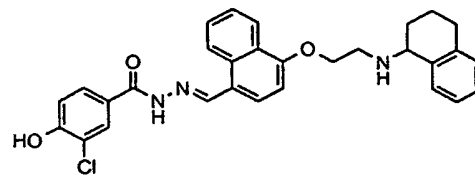
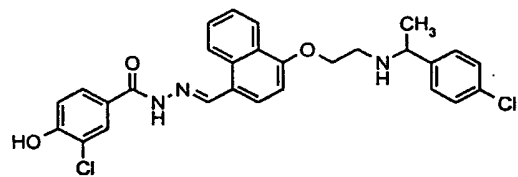
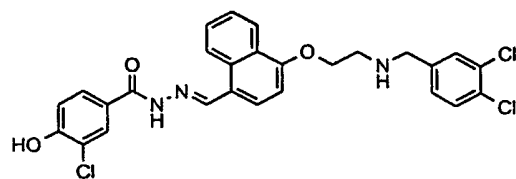
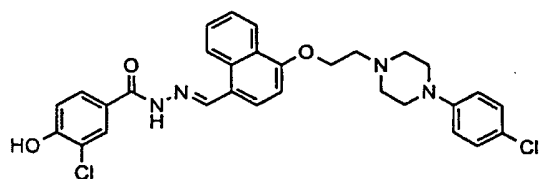
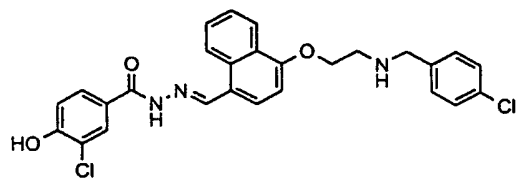
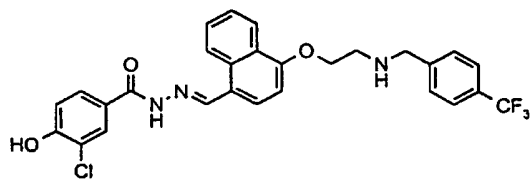
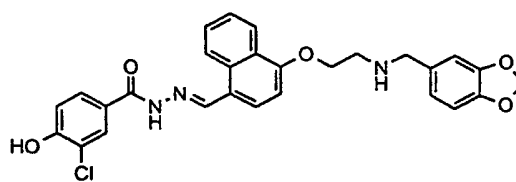
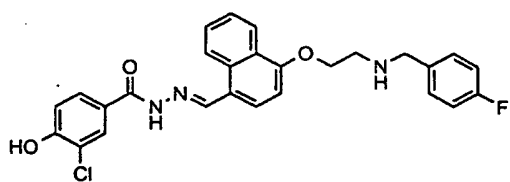




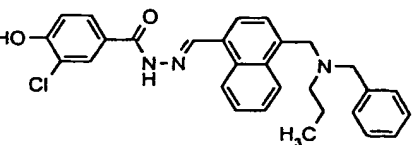
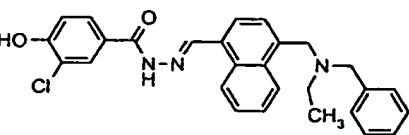
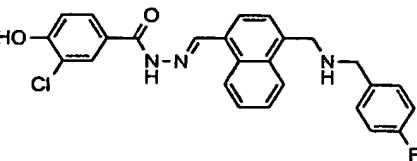
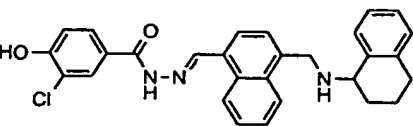
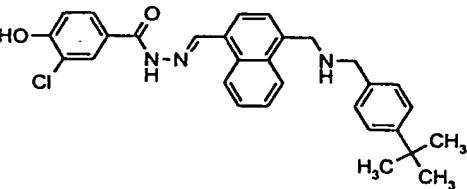
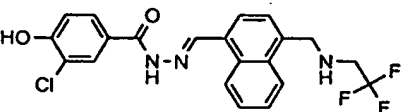
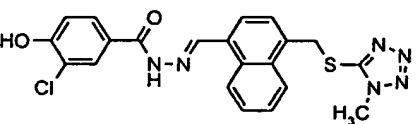
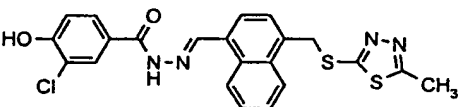
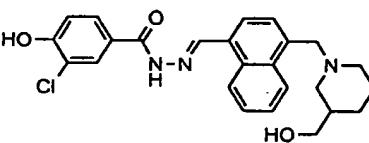
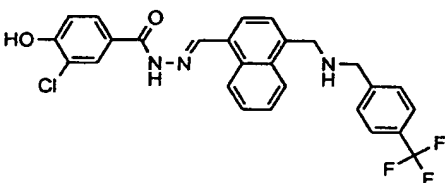
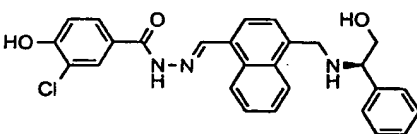
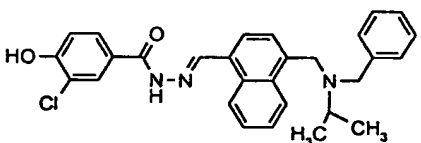
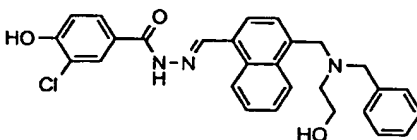
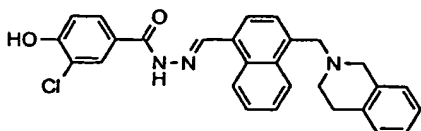
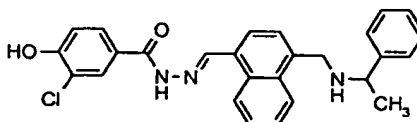
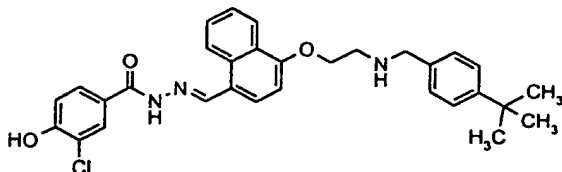
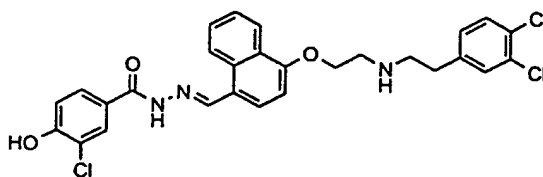
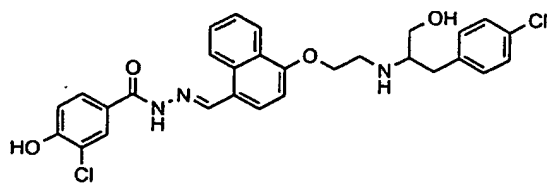
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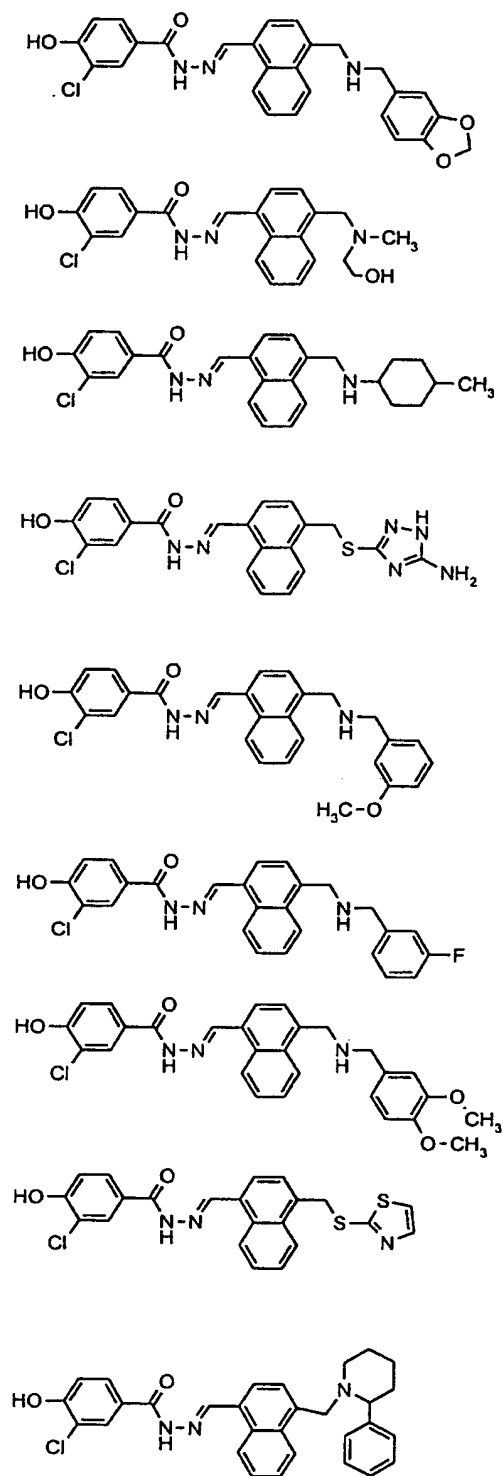


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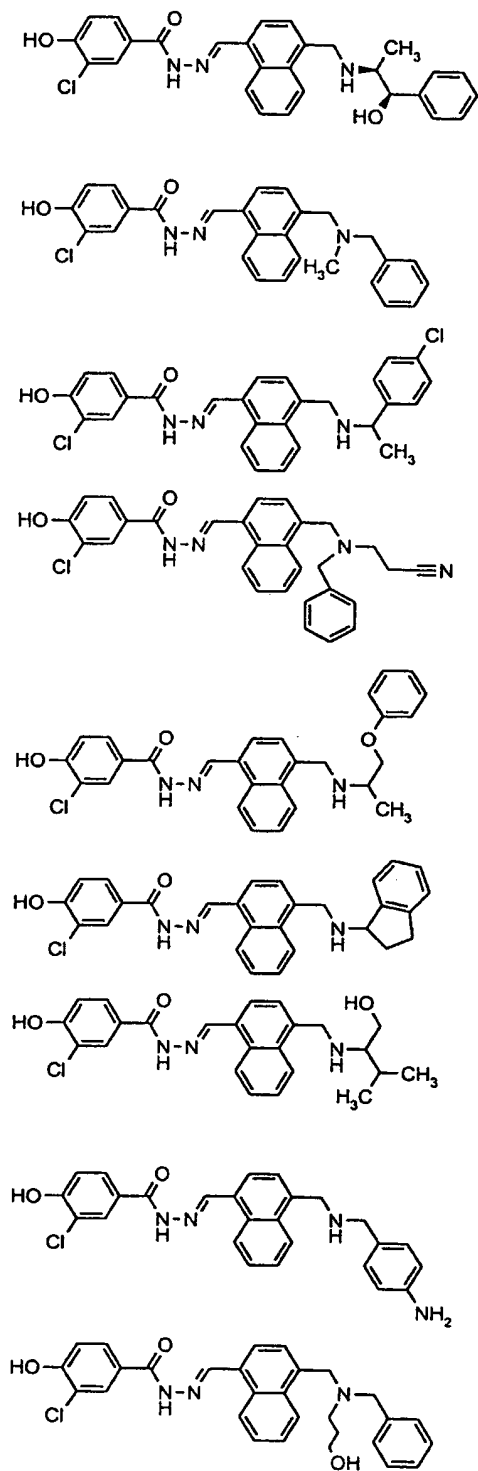


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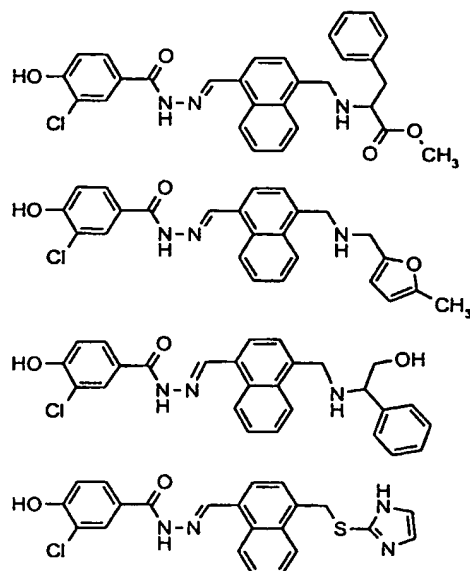
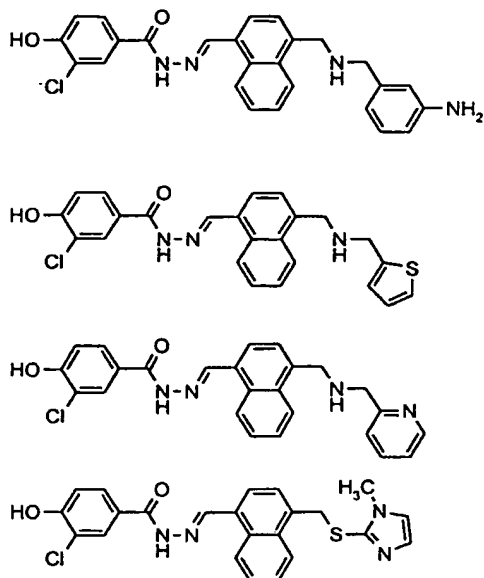




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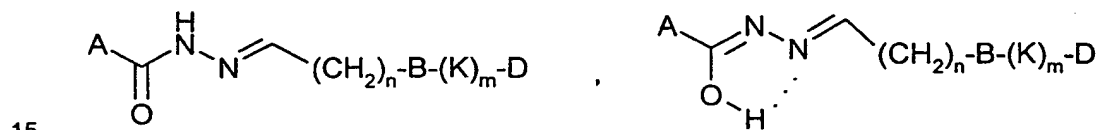
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The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included in the scope of the invention.

Furthermore, one or more carbon-carbon or carbon-nitrogen double bonds may be present in the compounds which brings about geometric isomers. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included in the scope of the invention.

Furthermore, the compounds of the present invention may exist in different tautomeric forms, eg the following tautomeric forms:



It is intended that any tautomeric forms which the compounds are able to form are included in the scope of the present invention.

Owing to their efficacy in antagonizing the glucagon receptor the present compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases.

5

Accordingly, the present compounds may be applicable for the treatment of hyperglycemia associated with diabetes of any cause or associated with other diseases and conditions, eg impaired glucose tolerance, insulin resistance syndromes, syndrome X, type I diabetes, type II diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, glucagonomas, acute pancreatitis, cardiovascular diseases, cardiac hypertrophy, gastrointestinal disorders, diabetes as a consequence of obesity etc. Furthermore, they may be applicable as diagnostic agents for identifying patients having a defect in the glucagon receptor, as a therapy to increase gastric acid secretions, to reverse intestinal hypomotility due to glucagon administration, to reverse catabolism and nitrogen loss in states of negative nitrogen balance and protein wasting including all causes of type I and type II diabetes, fasting, AIDS, cancer, anorexia, aging and other conditions, for the treatment of any of the above conditions or diseases post-operative or during surgery and for decreasing satiety and increasing energy intake. Thus, in a further aspect the present invention relates to a pharmaceutical composition comprising, as an active ingredient, at least one compound according to the present invention together with one or more pharmaceutically acceptable carriers or excipients.

20

The present invention furthermore relates to methods of treating type I or type II diabetes or hyperglycemia which methods comprise administering to a subject in need thereof an effective amount of a compound according to the invention.

25

Moreover, the present invention relates to a method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to the invention.

30

The present invention is also concerned with the use of a compound according to the invention for the manufacture of a medicament for treating type I or type II diabetes or hyperglycemia, or for lowering blood glucose in a mammal.

Pharmaceutical formulations and administration methods

The compounds according to the invention, which may also be referred to as an active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal), the oral route being preferred. It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the condition to be treated, and the chosen active ingredient.

The compounds of the invention are effective over a wide dosage range. A typical dosage is in the range of from 0.05 to about 1000 mg, preferably of from about 0.1 to about 500 mg, such as of from about 0.5 mg to about 250 mg for administration one or more times per day such as 1 to 3 times per day. It should be understood that the exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated as well as other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are on the order of about 1/2 the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of formula I contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of formula I with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids, for example: maleic, fumaric, benzoic, ascorbic, pantoic, succinic, bis-methylene salicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, pyruvic, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric or nitric acids. Physiologically acceptable salts of a

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compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

5 The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses.

For parenteral administration, solutions of the novel compounds of formula I in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic  
10 with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl  
15 ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by  
20 combining the novel compounds of formula I and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

25 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

30

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

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If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

- 5 A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	

Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

10

\*Acylated monoglyceride used as plasticizer for film coating.

- For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

- Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more other pharmacologically active compounds, e.g. an antidiabetic or other pharmacologically active material, including compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathological mechanism. Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S) which is incorporated herein by reference as well as orally active hypoglycaemic agents such as sulphonylureas, e.g. glibenclamide.

mide and glipizide; biguanides, e.g. metformin; benzoic acid derivatives, e.g. repaglinide; and thiazolidinediones, e.g. troglitazone and ciglitazone, as well as PPAR and RXR agonists.

## EXPERIMENTAL

### 5 Glucagon binding:

In the following section binding assays as well as functional assays useful for evaluating the efficacy of the compounds of the invention are described.

#### Glucagon Binding Assay (I)

10 Binding of compounds to the glucagon receptor was determined in a competition binding assay using the cloned human glucagon receptor.

In the screening setup, antagonism was determined as the ability of the compounds to inhibit the amount of cAMP formed in the presence of 5 nM glucagon.

15

For full characterization, antagonism was determined in a functional assay, measured as the ability of the compounds to right-shift the glucagon dose-response curve. Using at least 3 different antagonist concentrations, the  $K_i$  was calculated from a Schild plot.

Receptor binding was assayed using cloned human receptor (Lok et al, Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SstI restriction sites (Lok et al) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/ml G-418 and were shown to be stable for more than 40 passages. The  $K_d$  was shown to be 0.1 nM.

25 Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl, pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/l leupeptin (Sigma), 5 mg/l pepstatin (Sigma), 100 mg/l bacitracin (Sigma) and 15 mg/l recombinant aprotinin (Novo Nordisk)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation upon a layer of 30 41 w/v% sucrose at  $95.000 \times g$  for 75 min. The white band located between the two layers was

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diluted in buffer and centrifuged at 40.000 \* g for 45 min. The precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until required.

5 Glucagon was iodinated according to the chloramine T method (Hunter and Greenwood, Nature 194, 495 (1962)) and purified using anion exchange chromatography (Jørgensen et al, Hormone and Metab. Res. 4, 223-224 (1972). The specific activity was 460  $\mu\text{Ci}/\mu\text{g}$  on day of iodination. Tracer was stored at -18°C in aliquots and were used immediately after thawing.

Binding assays were carried out in triplicate in filter microtiter plates (MADV N65, Millipore).  
10 The buffer used in this assay was 25 mM HEPES pH 7.4 containing 0.1% human serum albumin (Sigma, grade V). Glucagon was dissolved in 0.05 M HCl, added equal amounts(w/w) of HSA and freeze-dried. On the day of use, it was dissolved in water and diluted in buffer to the desired concentrations.  
175  $\mu\text{l}$  of sample (glucagon or test compounds) was added to each well. Tracer (50.000 cpm)  
15 was diluted in buffer and 15  $\mu\text{l}$  was added to each well. 0.5  $\mu\text{g}$  freshly thawed plasma membrane protein diluted in buffer was then added in 15  $\mu\text{l}$  to each well. Plates were incubated at 25°C for 2 hours. Non specific binding was determined with  $10^{-6}$  M glucagon. Bound and unbound tracer were then separated by vacuum filtration (Millipore vacuum manifold). The plates were washed once with 150  $\mu\text{l}$  buffer/ well. The plates were air dried for a couple of hours,  
20 whereafter filters were separated from the plates using a Millipore Puncher. The filters were counted in a  $\gamma$  counter.

#### Functional Assay (I)

The functional assay was carried out in 96 well microtiter plates (tissue culture plates, Nunc).  
25 The resulting buffer concentrations in the assay were 50 mM tris/HCl, 1 mM EGTA, 1.5 mM  $\text{MgSO}_4$ , 1.7 mM ATP, 20  $\mu\text{M}$  GTP, 2 mM IBMX, 0.02% tween-20 and 0.1% HSA. pH was 7.4  
Glucagon and proposed antagonist were added in 35  $\mu\text{l}$  diluted in 50 mM tris/HCl, 1 mM EGTA, 1.85 mM  $\text{MgSO}_4$ , 0.0222 % tween-20 and 0.111 % HSA, pH 7.4. 20  $\mu\text{l}$  of 50 mM  
tris/HCl, 1 mM EGTA, 1.5 mM  $\text{MgSO}_4$ , 11.8 mM ATP, 0.14 mM GTP, 14 mM iso-buthyl-methyl-  
30 xanthine (IBMX) and 0.1% HSA, pH 7.4 was added. GTP was dissolved immediately before the assay.

124

50  $\mu$ l containing 5  $\mu$ g plasma membrane protein was added in a tris/HCl, EGTA,  $\text{MgSO}_4$ , HSA buffer (the actual concentrations were dependent upon the concentration of protein in the stored plasma membranes).

- 5 The total assay volume was 140  $\mu$ l. The assay was incubated for 2 hours at 37°C with continuous shaking. Reaction was terminated by addition of 25  $\mu$ l 0.5 N HCl. cAMP was measured by the use of a scintillation proximity kit (Amersham).

#### Glucagon Binding Assay (II)

- 10 Receptor binding was assayed using the cloned human receptor (Lok et al, Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SSt1 restriction sites (Lok et al) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/ml G-418 and were shown to be stable for more than 40 passages. The  $K_d$  was shown to be 0.1 nM.

15

- Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl), pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/l leupeptin (Sigma), 5 mg/l pepstatin (Sigma), 100 mg/l bacitracin (Sigma) and 15 mg/l recombinant aprotinin (Novo Nordisk)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation. The homogenate was resuspended and centrifuged again. The final precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until required.
- 20

- Binding assays were carried out in duplicate in polypropylene tubes or microtiter plates. The buffer used in this assay was 25 mM HEPES pH 7.4 containing 0.1% bovine serum albumin (Sigma, fraction V). Sample (glucagon (Bachem CA) or test compounds) was added to each tube or well. Tracer (~ 25000 cpm) was diluted in buffer and was added to each tube or well. 0.5  $\mu$ g freshly thawed plasma membrane protein diluted in buffer was then added in aliquots to each tube or well. Tubes or plates were incubated at 37°C for 1 hour. Non specific binding was determined with  $10^{-7}$  M glucagon. Bound and unbound tracer were then separated by vacuum filtration (Brandel). The tubes or wells were washed twice with buffer. The filters or plates were counted in a gamma counter.
- 25
- 30

Functional Assay (II)

The functional assay determined the ability of the compounds to antagonize glucagon-stimulated formation of cAMP in a whole-cell assay. The assay was carried out in borosilicate glass 12 x 75 tubes. The buffer concentrations in the assay were 10 mM HEPES, 1 mM EGTA, 1.4 mM MgCl<sub>2</sub>, 0.1 mM IBMX, 30 mM NaCl, 4.7 mM KCl, 2.5 mM NaH<sub>2</sub>PO<sub>4</sub>, 3mM glucose and 0.2% BSA. The pH was 7.4. Loose whole cells (0.5 ml, 10<sup>6</sup>/ml) were pretreated with various concentrations of compounds for 10 min at 37°C, then challenged with glucagon for 20 min. Some aliquots (500 µL) of cells were treated with test compounds (55 uL) alone to test for agonist activity. The reactions were terminated by centrifugation, followed by cell lysis with the addition of 500 µl 0.1% HCl. Cellular debris was pelleted and the supernatant containing cAMP evaporated to dryness. cAMP was measured by the use of an RIA kit (NEN, NEK-033). Some assays were carried out utilizing the adenylate cyclase FlashPlate system from NEN.

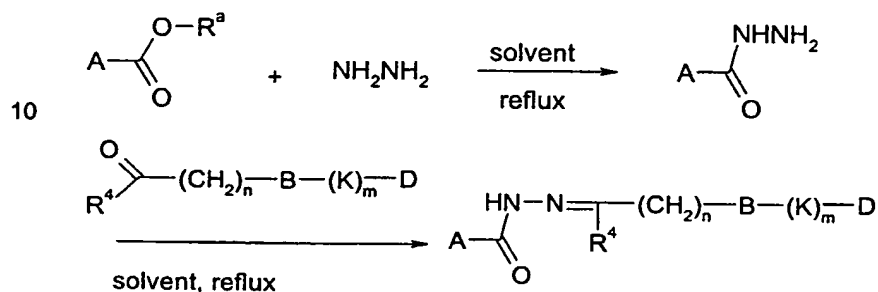
Synthesis methods

The following synthesis protocols refer to intermediate compounds and final products identified in the specification and in the synthetic schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of the glucagon antagonists of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

General procedures for the preparation of alkylidene hydrazides:

The compounds of general formula I may be prepared according to one embodiment of the invention, the alkylidene hydrazides of general formula II, as indicated in Scheme I, that is, by  
 5 converting an ester of a carboxylic acid, for example, an aromatic acid to a hydrazide derivative and further reacting that product compound with a substituted aldehyde or ketone to yield a substituted alkylidene hydrazide.

SCHEME I



wherein A, B, K, D, m, n and R<sup>4</sup> are as defined for formula I and R<sup>a</sup> is lower alkyl.

15 General procedure for the synthesis of precursor hydrazides A-(C=O)-NHNH<sub>2</sub>:

The reaction is known (Org. Syn., Coll. Vol. II, A.H. Blatt, ed., John Wiley & Sons, New York, 1943, p. 85; Org. Syn., Coll. Vol. IV, N. Rabjohn, ed., John Wiley & Sons, New York, 1963, p. 819) and is generally performed by stirring the corresponding ester (either methyl, ethyl or other lower alkyl ester) with 2-10 molar excess of hydrazine in the presence of a solvent such  
 20 as ethyl alcohol, methyl alcohol, isopropyl or tert-butyl alcohol or tetrahydrofuran, dioxane, DMSO, ethylene glycol, ethylene glycol dimethyl ester, benzene, toluene or a mixture of the above solvents or, in the absence of a solvent where excess of hydrazine acts as a solvent. The reactions are performed between 0°C to 130°C, preferably between 20°C to 100°C, most preferably at or about the reflux temperature of the solvent. The reactions are preferably conducted under an inert atmosphere such as N<sub>2</sub> or Ar. When the reaction is complete as judged  
 25 by disappearance of the starting ester by TLC or HPLC, the solvent may be removed by concentration at atmospheric or reduced pressure.

The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be  
5 purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent. The corresponding fractions are concentrated either at atmospheric pressure or in vacuo to provide the pure aroyl hydrazide.

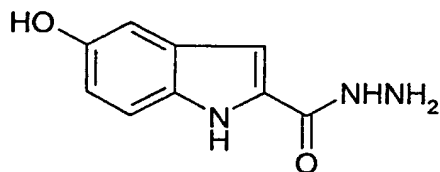
Preparation of aromatic acid hydrazides:

10 The methyl or ethyl ester of the corresponding aromatic acid, such as for example a substituted benzoic acid ester, is dissolved in ethanol and hydrazine (5 eq) is added. The reaction is refluxed overnight under nitrogen. Upon cooling the substituted hydrazide derivative usually precipitates. After filtration the product is usually recrystallized from hot methanol, ethanol or isopropyl alcohol. In cases where the hydrazide does not precipitate, the reaction is concentrated under vacuo and chromatographed over silica gel using dichloromethane/methanol as  
15 the eluent. Specific examples illustrating the preparation of aromatic hydrazides are provided below.

Preparation of 5-hydroxyindole-2-carboxylic acid hydrazide:

20 To a sample of ethyl 5-hydroxyindole-2-carboxylate (5g, 24 mmol), dissolved in ethanol (250 mL) was added hydrazine (4 mL, 121 mmol). The reaction was refluxed overnight under nitrogen. Upon cooling the reaction vessel, the desired product crystallized. The white solid was isolated by filtration. Recrystallization from hot ethanol gave the 5-hydroxyindole-3-carboxylic acid hydrazide in 85% yield.

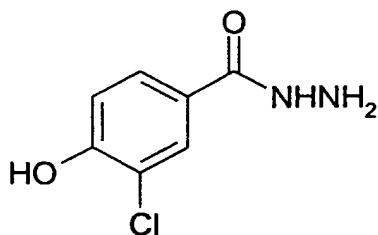
25



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.38 (s, 2H); 6.62 (dd, 1H); 6.76 (dd, 2H); 7.13 (d, 1H); 8.70 (s, 1H); 9.57 (s, 1H); 11.21 (s, 1H); MS (FAB):  $m/z$  192 ( $M+H$ ) $^+$ .

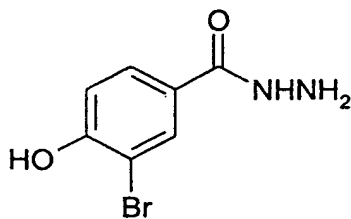
Preparation of 3-chloro-4-hydroxybenzoic acid hydrazide:

To a sample of methyl 3-chloro-4-hydroxybenzoate (2 g) dissolved in ethanol (50 mL) was added hydrazine (1.8 mL). The reaction was refluxed overnight under nitrogen. Upon cooling the reaction vessel, the desired product crystallized out of solution. The white solid was isolated by filtration. Recrystallization from hot ethanol gave the 3-chloro-4-hydroxybenzoic acid hydrazide in 60% yield.



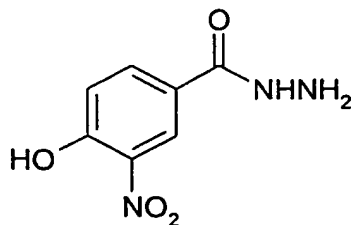
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.49 (broad s, 2H), 7.05 (dd, 1H), 7.71 (dd, 1H), 7.89 (d, 1H), 9.669 (s, 1H), 10.72 (broad s, 1H).

By use of the above methodology, other hydrazides useful as intermediates in preparing the compounds of the invention are prepared, for example:



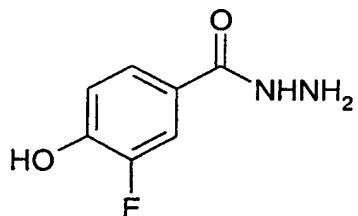
3-Bromo-4-hydroxybenzoic acid hydrazide

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.95 (s, 1H), 9.65 (d, 1H), 9.61 (broad s, 1H), 6.95 (d, 1H), 4.40 (broad s, 2H); MS m/z 233.1.



## 3-Nitro-4-hydroxybenzoic acid hydrazide

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.28 (broad s, 1H), 8.28 (s, 1H), 7.52 (d, 1H), 6.41 (d, 1H). MS  $m/z$  198.

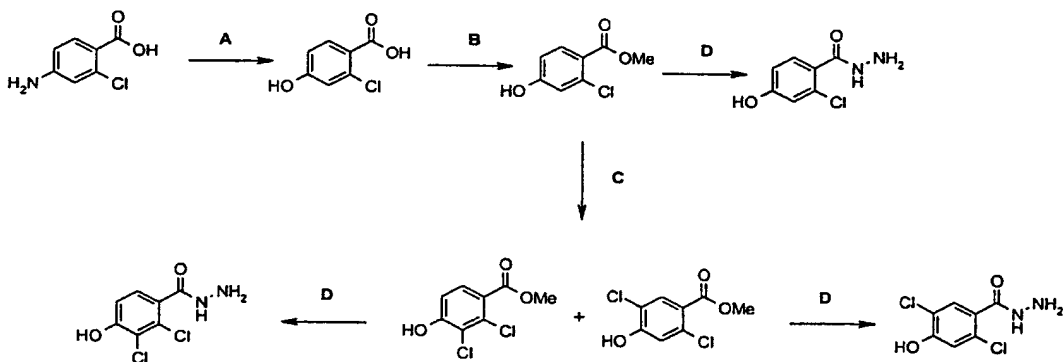


5

## 3-Fluoro-4-hydroxybenzoic acid hydrazide

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.45 (broad s, 1H), 7.5 (d, 1H), 7.43 (d, 1H), 6.85 (t, 1H), 5.55 (broad s, 3H).

10 **Preparation of 2-chloro-4-hydroxybenzoic acid hydrazide, 2,3-dichloro-4-hydroxybenzoic acid hydrazide and 2,5-dichloro-4-hydroxybenzoic acid hydrazide.**



15 **Preparation of 2-chloro-4-hydroxybenzoic acid hydrazide:**

## Step A:

4-amino-2-chlorobenzoic acid (10 g, 58 mmol) was dissolved in  $\text{H}_2\text{SO}_4$  (12 N, 120 mL) with heating. After cooling the solution in an ice-bath aqueous  $\text{NaNO}_2$  (2.5 M, 25 mL) was added dropwise such that the internal temperature remained at 5 °C. Urea was added to the mixture for after stirring for 15 minutes to destroy excess  $\text{NaNO}_2$  (monitored by starch iodine test).

20

CuSO<sub>4</sub> (100-200 mg) was added and the mixture was heated to 90 °C until evolution of gas stopped. After cooling, the mixture was extracted with ethyl ether (3x). The combined organic fractions were extracted with 3N NaOH (3x). The combined aqueous layer was acidified with conc. HCl and the product was extracted with ethyl ether (3x). The organic fractions  
5 were washed with water, brine, and dried over MgSO<sub>4</sub>. The crude product was introduced into a silica gel column and eluted with ethyl acetate/hexane (1/1) to afford 2-chloro-4-hydroxybenzoic acid.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 6.97 (dd, 1H), 7.05 (d, 1H), 7.95 (d, 1H), 10.90 (brd s, 1H).

Step B:

To a solution 2-chloro-4-hydroxybenzoic acid in anhydrous methanol was added thionyl chloride (1.5 eq). After stirring the solution at room temperature for 16 hours, the solvent was evaporated. The residue was taken up in ethyl acetate and washed with saturated aqueous  
15 sodium bicarbonate, water, brine, and dried over MgSO<sub>4</sub> and concentrated in vacuo to give methyl 2-chloro-4-hydroxybenzoate.

Step C:

To a solution of methyl 2-chloro-4-hydroxybenzoate (13.6 g, 73.1 mmol) in acetic acid (300  
20 mL) was added N-chlorosuccinimide (9.8 g, 73.7 mmol). The solution was refluxed for 24 h and the solvent was evaporated under vacuo. The residue was taken up in chloroform, washed with water, brine, dried over magnesium sulfate, filtered and concentrated. Methyl 2,3-dichloro-4-hydroxybenzoate precipitated out of ethyl acetate. Chromatography of the residue using ethyl acetate/hexane (1/9 to 3/7) afforded methyl 2,5-dichloro-4-  
25 hydroxybenzoate (1.4 g, 60%) as well as an additional batch of methyl 2,3-dichloro-4-hydroxybenzoate isomer (total of 8.4 g, 10%).

Methyl 2,3-dichloro-4-hydroxybenzoate:

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 3.81 (s, 3H), 7.02 (d, 1H), 7.70 (d 1H), 11.52 (s, 1H); MS (APCI):  
30 221, 223.

Methyl 2,5-dichloro-4-hydroxybenzoate:

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.90 (s, 3H), 6.00 (s, 1H), 7.14 (s, 1H), 7.27 (s, 1H), 7.96 (s, 1H); MS (APCI): 221.9.

5 Step D:

The title compound was prepared according to the general procedure for the synthesis of precursor hydrazides A-(C=O)-NHNH<sub>2</sub>.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 6.82 (dd, 1H), 6.90 (d, 1H), 7.79 (d, 1H), 10.68 (brd s, 1H).

10

**Preparation of 2,3-Dichloro-4-hydroxybenzoic acid hydrazide and 2,5-dichloro-4-hydroxybenzoic acid hydrazide (step D):**

The 2,3-dichloro-4-hydroxybenzoic acid hydrazide was prepared from the methyl 2,3-dichloro-4-hydroxybenzoate above according to the general procedure for the synthesis of precursor hydrazides A-(C=O)-NHNH<sub>2</sub> with the exception that pentanol was the solvent of choice. The product was purified via silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>/MeOH (95/5 to 80/20), yield = 50%.

20 2,5-dichloro-4-hydroxybenzoic acid hydrazide was prepared in a similar way starting from 2,5-dichloro-4-hydroxybenzoate.

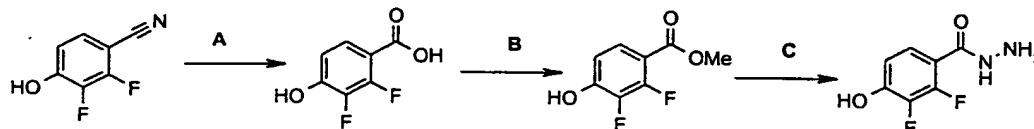
**2,3-Dichloro-4-hydroxybenzoic acid hydrazide:**

25 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 4.41 (brd s, 2H), 6.99 (t, 1H), 7.37 (s, 1H), 9.46 (s, 1H), 11.04 (s, 1H).

**2,5-Dichloro-4-hydroxybenzoic acid hydrazide:**

30 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 4.48 (brd s, 3H), 6.92 (d, 2H), 7.18 (d, 2H), 9.45 (brd s, 1H).

**Preparation of 2,3-difluoro-4-hydroxybenzoic acid hydrazide:**



#### Step A:

- 5 A mixture of 2,3-difluoro-4-cyanophenol (1 g, 6.45 mmol) in water (8 mL),  $\text{H}_2\text{SO}_4$  (8 mL), and acetic acid (8 mL) was refluxed for 48 hours. The solvents were removed by rotary evaporation to give a slurry which was poured onto ice. The product precipitated out of solution and filtered. The solid was washed with water and dried to give 2,3-difluoro-4-hydroxybenzoic acid (800 mg, 71%).

10

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  6.87 (t, 1H), 7.60 (t, 1H), 11.28 (s, 1H), 12.53 (brd s, 1H).

#### Step B:

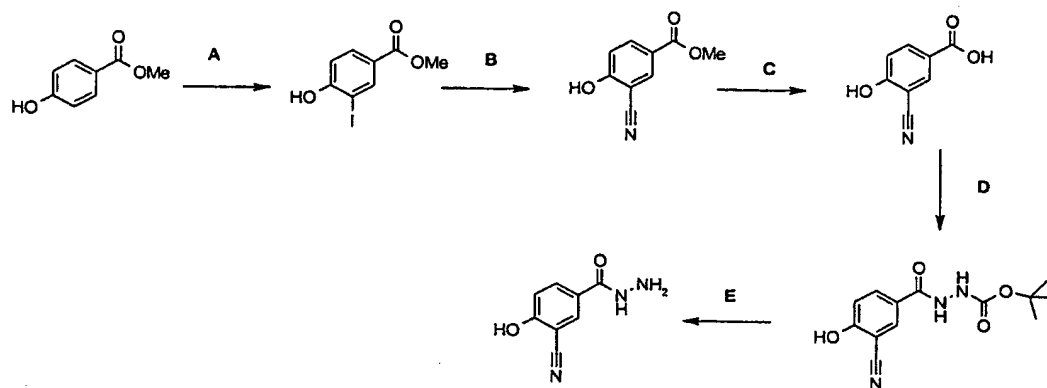
- 15 To the 2,3-difluoro-4-hydroxybenzoic acid (800 mg, 5.1 mmol) dissolved in anhydrous methanol (50 mL) was added thionyl chloride (0.55 mL, 7.3 mmol). After stirring the solution at room temperature for 16 hours, the solvent was evaporated. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, brine, and dried over  $\text{MgSO}_4$  to give methyl 2,3-difluoro-4-hydroxybenzoate (540 mg, 62%).

- 20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.92 (s, 3H), 6.34 (brd s, 1H), 6.82 (dt, 1H), 7.68 (dt, 1H).

#### Step C:

- 25 The 2,3-difluoro-4-hydroxybenzoic acid hydrazide was prepared from the methyl 2,3-difluoro-4-hydroxybenzoate above according to the general procedure for the synthesis of precursor hydrazides  $\text{A}-(\text{C}=\text{O})-\text{NHNH}_2$ . The product was purified via silica gel column chromatography using  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (95/5 to 80/20) to afford the title compound.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.48 (s, 2H), 6.80 (m, 1H), 7.22 (m, 1H), 9.36 (s, 1H), 10.89 (s, 1H); MS (APCI): 189.

**Preparation of 3-cyano-4-hydroxybenzoic acid hydrazide, trifluoroacetate:****Step A:**

Methyl-4-hydroxybenzoate (35.5 g, 0.233 mol) was dissolved in 200 mL of warm (65 °C) acetic acid. A solution of iodine monochloride (37.8 g, 0.233 mol) in 50 mL of acetic acid was added slowly (40 minutes) to the methyl-4-hydroxybenzoate solution, while maintaining a temperature of 65 °C and vigorous stirring. The product crystallizes from solution upon cooling to room temperature and standing overnight. The crystals were collected on a filter, washed with water, then dried under vacuum. Methyl-4-hydroxy-3-iodobenzoate was obtained as white crystals (28.6 g, 44%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.79 (s, 3H), 6.95 (d, J = 8.3, 1H), 7.81 (dd, J = 8.3, 2.2, 1H), 8.22 (d, J = 2.2, 1H); <sup>13</sup>C NMR (DMSO- D<sub>6</sub>) δ 52.8, 85.2, 115.5, 123.0, 132.0, 141.0, 161.9, 165.6.; MS (APCI, neg): 277.

**Step B:**

Methyl-4-hydroxy-3-iodobenzoate (2.00 g, 7.2 mmol) was dissolved into 5 mL of dry DMF. Copper(I) cyanide (0.72 g, 8.0 mmol) and a small crystal of sodium cyanide was added. The mixture was flushed with nitrogen, placed in an oil heating bath (100-110 °C), and stirred overnight. TLC indicated nearly complete reaction. The mixture was cooled and the solids removed by filtration. The solids were extracted with DMF (3 mL). The filtrate and washings were taken up in 100 mL of ethyl acetate, then washed with 3 portions of saturated sodium chloride solution. The solids and aqueous washings were combined, and shaken with a

mixture of 50 mL of ethyl acetate and a ferric chloride solution (4 g of hydrated ferric chloride in 7 mL of conc. hydrochloric acid). The ethyl acetate layers were combined, washed with brine containing sodium metabisulfite, dried over sodium sulfate, filtered, and the solvent removed in vacuo. The resulting solids were purified by flash chromatography on silica gel (20% ethyl acetate/ hexane) to afford methyl-3-cyano-4-hydroxybenzoate, 0.93g (73%).

<sup>1</sup>H NMR (DMSO- D<sub>6</sub>): δ 3.79 (s, 3H), 7.07 (d, J = 8.7, 1H), 8.02 (dd, J = 8.7, 1.9, 1H), 8.10 (d, J = 1.9, 1H).

10 Step C:

Methyl-3-cyano-4-hydroxybenzoate (2.71g, 15.3 mmol) was dissolved in 50 mL of THF. The solution was chilled in an ice bath, and 2.0M potassium hydroxide (17 mL, 34 mmol) was added dropwise. The resulting mixture was stirred at room temperature overnight. TLC indicated complete reaction. The THF was removed by rotary evaporation. The aqueous residue was acidified with aqueous trifluoroacetic acid and purified by reverse-phase HPLC (C-18, 0.1% TFA in water and acetonitrile). 3-Cyano-4-hydroxybenzoic acid was obtained as a white powder (2.1g, 84%) after lyophilization.

<sup>1</sup>H NMR (DMSO- D<sub>6</sub>): δ 7.09 (d, J = 9.0, 1H), 8.00 (dd, J = 9.0, 2.3, 1H), 8.07 (d, J = 2.3, 1H) 12.50 (br s, 2H); MS (APCI, neg): 162. IR: 2252 cm<sup>-1</sup>, CN.

Step D:

3-Cyano-4-hydroxybenzoic acid (1.88g, 11.5 mmol) was dissolved in 20 mL of methylene chloride/DMF (1/1) and chilled in an ice-bath. Diisopropylethylamine (12 mL, 69 mmol), t-butyl carbazate (1.76g, 13.3 mmol), and PyBroP (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 6g, 12.9 mmol) were added, and the mixture was stirred to form a clear solution. The solution stood in the refrigerator overnight. TLC indicated that the reaction was not complete, so additional diisopropylethylamine (22 mL, 127 mmol), t-butyl carbazate (0.85g, 6.4 mmol) and PyBroP (3.0g, 6.4 mmol) were added. After 8 more hours at 0 °C, the reaction was worked up as follows. The solution was reduced by rotary evaporation. The remaining DMF solution was diluted with 100 mL of ethyl acetate, and washed with several portions of 0.1 M HCl (until the wash remained acidic to litmus paper). The ethyl acetate layer was further washed with 3 portions of brine, dried over magnesium sulfate, filtered, and

reduced to an oil in vacuo. The oil was purified by chromatography on silica gel (6:4 hexane:ethyl acetate) to afford tert-butyloxycarbonyl (3-cyano-4-hydroxy)benzoic acid hydrazide as a white solid (1.8g, 56%).

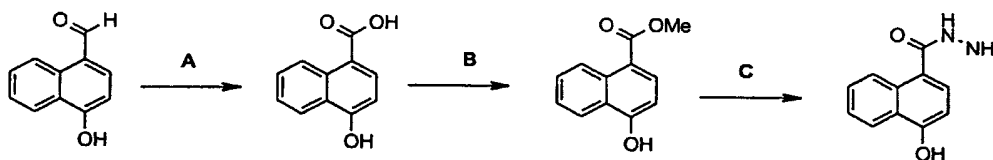
- 5  $^1\text{H}$  NMR (DMSO-  $\text{D}_6$ ):  $\delta$  1.42 (s, 9H), 7.09 (d,  $J$  = 8.7, 1H), 7.98 (m, 1H), 8.11 (br s, 1H), 8.92 (s, 1H), 10.15 (s, 1H), 11.73 (br s, 1H); MS (APCI, neg): 276; IR: 2232  $\text{cm}^{-1}$ , CN.

Step E:

- 10 The Boc-hydrazide (1.8g, 6.5 mmol) was suspended in 50 mL of chloroform and cooled in an ice-bath. Trifluoroacetic acid was added with stirring, and the resulting solution stood for 4 hours at 0 °C. TLC indicated complete reaction. Solvent and excess TFA were removed by rotary evaporation. The remaining oil was purified by reverse-phase liquid chromatography (Aquasil C-18 column, water/acetonitrile/0.1% TFA). The title compound was obtained as a  
15 white solid (0.24 g, 13%).

$^1\text{H}$  NMR (DMSO-  $\text{D}_6$ ):  $\delta$  7.16 (d,  $J$  = 9.0, 1H), 8.00 (dd,  $J$  = 1.5, 9.0, 1H), 8.14 (d,  $J$  = 1.5, 1H), 10.47 (br s, 5H); MS (APCI, neg): 176.

20 Preparation of 4-hydroxynaphthoic acid hydrazide:



Step A:

- 25 Silver nitrate (17 g, 0.1 mol) was dissolved in water (10 mL) and treated with 1 N NaOH (300 mL, 0.3 mol). The brown precipitate which was formed was stirred for 30 minutes and the supernatant was decanted. The brown silver oxide was washed with additional volumes of water (3x).

- To the silver oxide above was added 1N NaOH (150 mL) and 4-hydroxynaphthaldehyde (1 g, 6 mmol)). The mixture was heated to 70 °C for 10 minutes after which additional amounts of 4-hydroxynaphthaldehyde (5.5 g, 32 mmol) was added in portions. The mixture was kept at 80 °C for 16 hours. TLC analysis indicated incomplete conversion. An additional portion
- 5 of silver oxide was prepared as above and added to the reaction mixture. After heating the mixture for an additional 6 hours, the mixture was cooled and acidified with 1N HCl. The aqueous layer was extracted with ethyl acetate (3x) and upon concentration 4-hydroxynaphthoic acid precipitated (3.7 g, 60%) out of solution.
- 10 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 6.69 (d, 1H), 7.28 (t, 1H), 7.39 (t, 1H), 7.93 (d, 1H), 8.03 (d, 1H), 8.82 (d, 1H), 10.82 (s, 1H), 12.29 (s, 1H).

Step B:

- To a solution 4-hydroxynaphthoic acid in anhydrous methanol at 0 °C was added thionyl chloride (1.5 eq). After stirring the solution at room temperature for 16 hours, the solvent
- 15 was evaporated. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, brine, and dried over MgSO<sub>4</sub> to give methyl 4-hydroxynaphthoate.
- 20 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.87 (s, 3H), 6.92 (d, 1H), 7.53 (t, 1H), 7.65 (t, 1H), 8.13 (d, 1H), 8.26 (d, 1H), 8.93 (d, 1H), 11.16 (s, 1H).

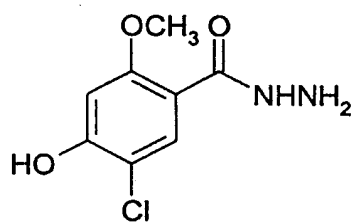
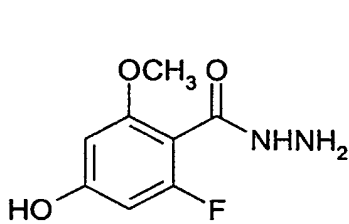
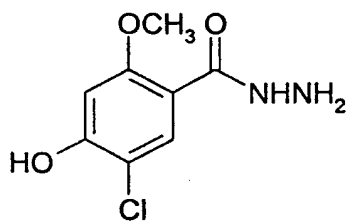
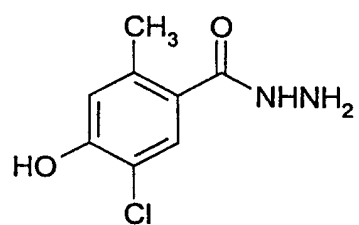
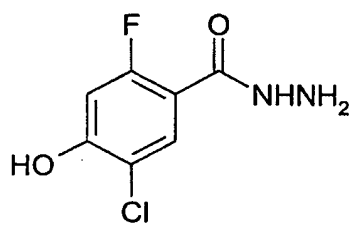
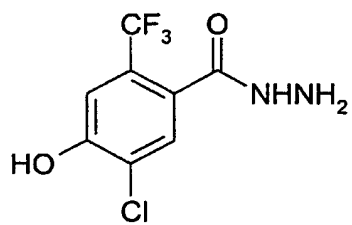
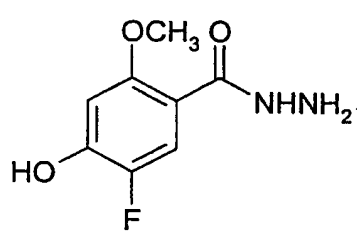
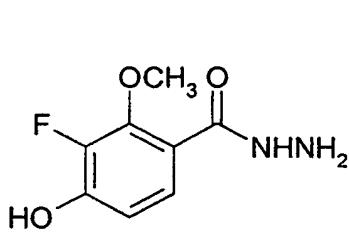
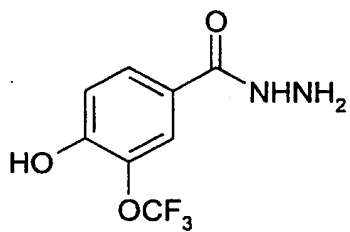
Step C:

- The title compound was prepared from methyl 4-hydroxynaphthoate according to the procedure for the synthesis of precursor hydrazides A-(C=O)-NHNH<sub>2</sub>.
- 25

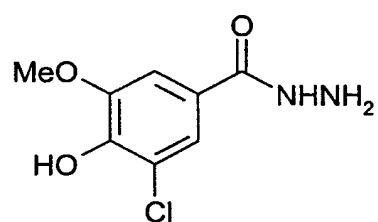
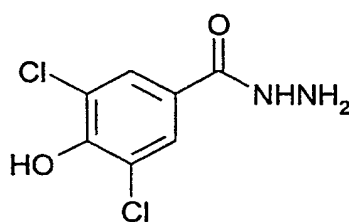
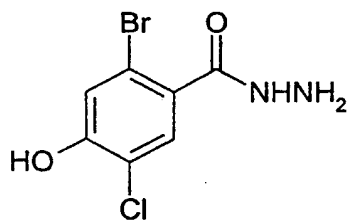
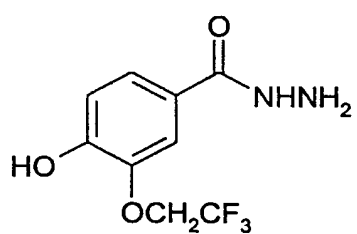
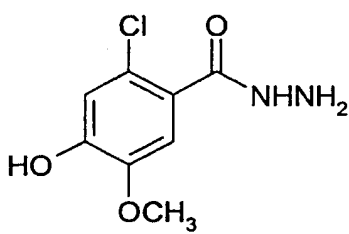
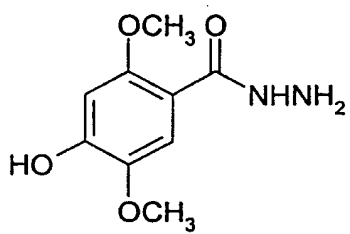
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 6.60 (d, 1H), 7.28 (m, 3H), 7.95 (d, 1H), 8.07 (d, 1H), 9.25 (brd s, 1H).

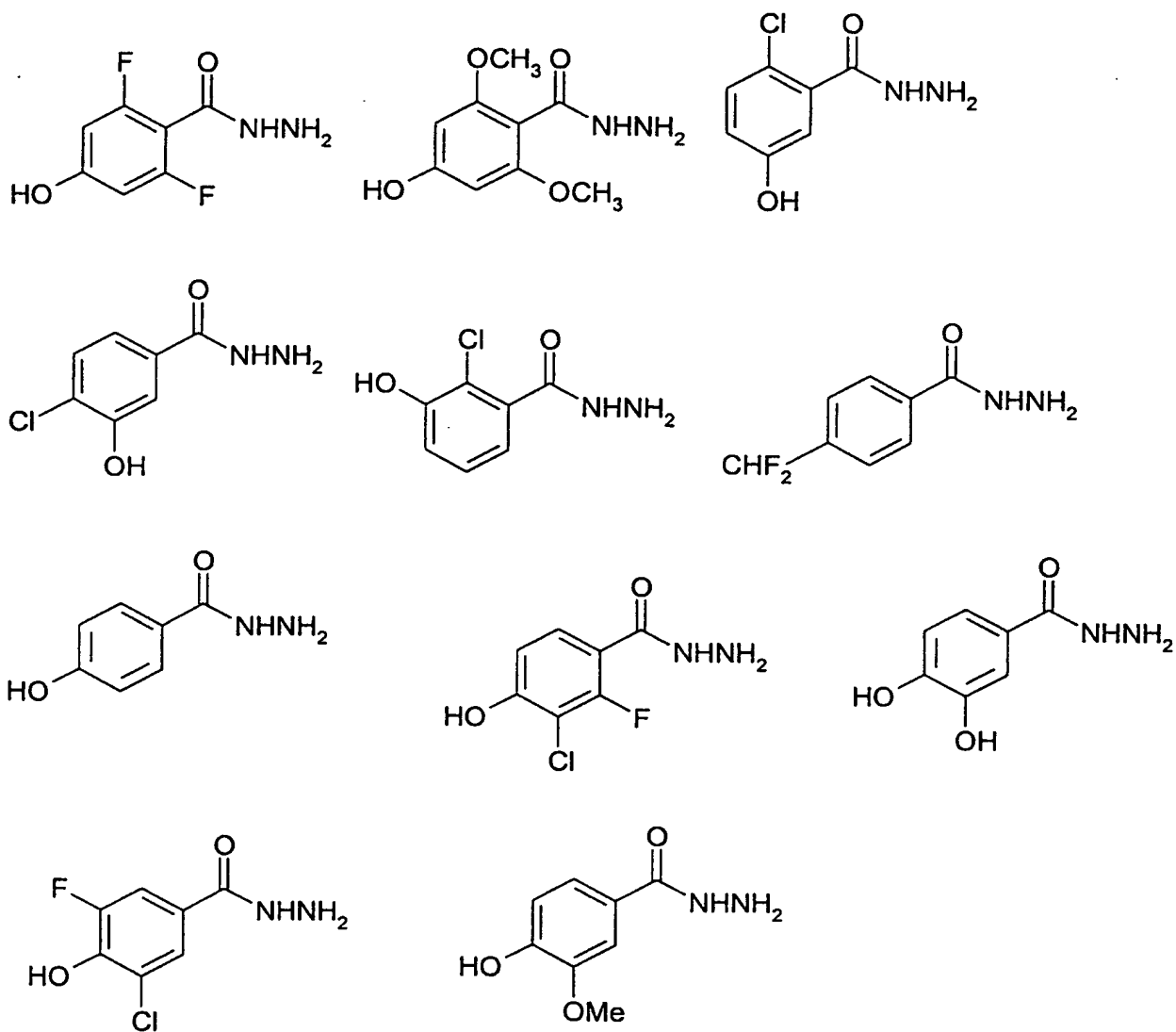
30

Moreover, by use of the above methodology, the following hydrazides useful as intermediates in preparing the compounds of the invention may be prepared:



5





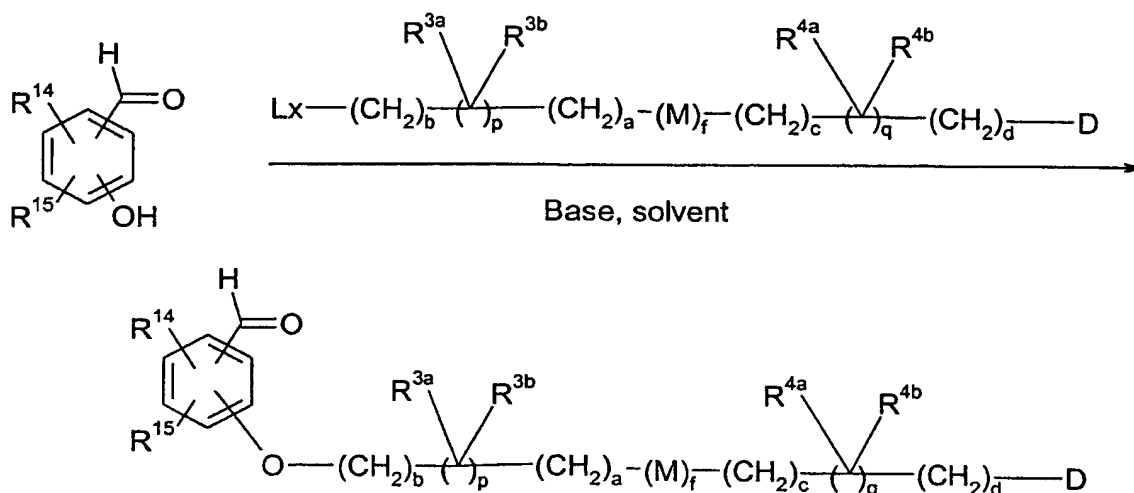
5

General procedure for the synthesis of ether-substituted aryl-aldehydes:

The ether-linked aldehydes may be prepared by O-alkylation of the corresponding phenolic compounds using various electrophilic alkylating agents that introduce the  $-(K)_m-D$  moiety as defined above in a reaction generally known as Williamson ether synthesis (H. Feuer, J. Hooz in *The Chemistry of the Ether Linkage*, S. Patai Ed., Wiley, New York 1967, p. 446-460).

10

## SCHEME II



- 5 wherein Lx is a leaving group such as -Cl, -Br, -I, -OSO<sub>2</sub>CH<sub>3</sub>, -OSO<sub>2</sub>p-tolyl or -OSO<sub>2</sub>CF<sub>3</sub>; and

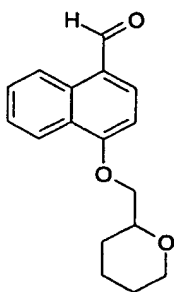
$R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ , a, b, c, d, f, p, q, D, M,  $R^{14}$  and  $R^{15}$  are as defined for formula I.

- 10 According to Scheme II an ether-substituted aryl-aldehyde can be prepared by stirring hydroxybenzaldehydes or hydroxynaphthaldehydes in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, water or a compatible mixture of two or more of the above solvents with an equimolar amount of an alkyl halide or an aryl-lower alkyl halide and in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or tert-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-collidine or benzyldimethylammonium methoxide or hydroxide. The reaction can be performed at 0°C to 150°C, preferably at 20°C to
- 20 100°C and preferably in an inert atmosphere of N<sub>2</sub> or Ar. When the reaction is complete the mixture is filtered, concentrated in vacuo and the resulting product optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol,

ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture. Specific examples illustrating the preparation of ether-substituted aryl-aldehydes are provided below.

Preparation of 4-(2-tetrahydropyranylmethoxy)-1-naphthaldehyde:

- 5 A mixture of 4-hydroxynaphthaldehyde (1 g, 5.8 mmol), 2-bromomethyl tetrahydropyran (1 g, 5.8 mmol) and powdered  $K_2CO_3$  (1.2 g, 8.7 mmol) in dimethyl formamide was stirred at 60°C overnight. The mixture was taken up in water and ethyl acetate. The organic layer was separated and washed with water, brine, dried over  $MgSO_4$ , filtered, and concentrated. The product was purified by silica gel column chromatography using ethyl acetate/hexane.

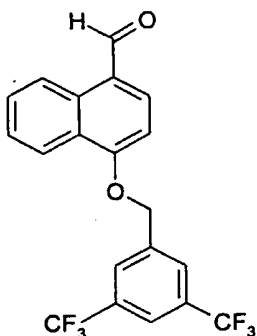


10

$^1H$  NMR ( $DMSO-d_6$ ):  $\delta$  1.48 (m, 4H), 1.74 (d, 1H), 1.84 (m, 1H), 3.44 (m, 1H), 3.78 (m, 1H), 3.92 (d, 1H), 4.23 (m, 2H), 7.17 (d, 1H), 7.64 (t, 1H), 7.74 (t, 1H), 8.11 (d, 1H), 8.27 (d, 1H), 9.22 (d, 1H), 10.17 (s, 1H).

- 15 Preparation of 4-[(3,5-bis-trifluoromethyl)benzyloxy]-1-naphthaldehyde:

A mixture of 4-hydroxynaphthaldehyde (1 g, 5.8 mmol), 3,5-bis-trifluoromethylbenzylbromide (1.8 g, 5.8 mmol), and powdered  $K_2CO_3$  (1.2 g, 8.7 mmol) was stirred in acetone (40 mL) overnight. The mixture was poured onto 200 mL of ice-chips and stirred until the ice melted. The yellow precipitate, 4-[(3,5-bis-trifluoromethyl)benzyloxy]-1-naphthaldehyde, was collected and  
20 dried.

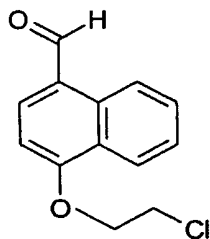


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  5.58 (s, 2H), 7.07 (d, 1H), 7.22 (d, 1H), 7.63 (t, 1H), 7.69 (t, 1H), 7.79 (d, 1H), 7.86 (d, 1H), 7.99 (s, 1H), 8.14 (s, 1H), 8.30 (s, 3H), 8.94 (s, 1H), 8.97 (d, 1H), 11.0 (broad s, 1H), 11.69 (s, 1H); MS (ESI)  $m/z$  675.2 ( $\text{M}+\text{H}$ ) $^+$ .

5

Preparation of 4-(2-chloroethoxy)-1-naphthaldehyde:

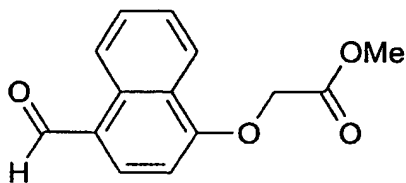
To a solution of 4-hydroxy-1-naphthaldehyde (8.6 g, 50 mmoles) and potassium carbonate (13.8 g, 100 mmoles) in N,N-dimethylformamide (DMF) (40 mL) was added 1-bromo-2-chloroethane (7.4 g, 50 mmoles). The mixture was heated at 60°C overnight. The solution  
 10 was diluted with ethyl acetate (500 mL), extracted with water and brine. The organic layer was dried over magnesium sulfate and the solvent was evaporated to obtain 12.1 g product (52 % yield).



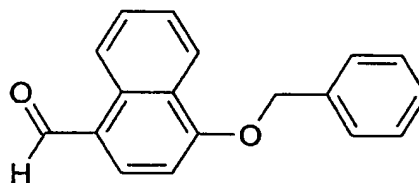
15 MS (CI): 403, 405, 407.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.2 (s, 1H), 9.3 (d, 1H), 8.35 (d, 1H), 7.85 (d, 1H), 7.65 (m, 1H), 7.5 (m, 1H), 7.1 (d, 1H), 4.35 (t, 2H), 4.15 (t, 2H).

The products were used as such in further transformations.

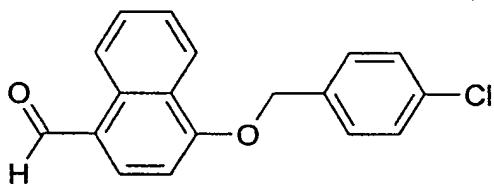
By application of the above methodology the following substituted aldehyde intermediates were synthesized:



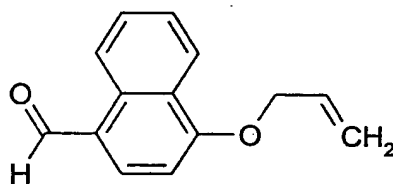
4-carbomethoxymethoxy-1-naphthaldehyde  
m.p.: 115-116°C



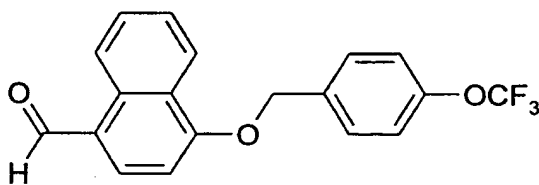
4-benzyloxy-1-naphthaldehyde



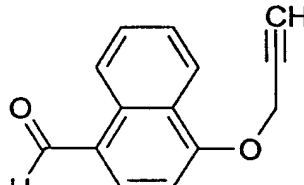
4-(4-chlorobenzyloxy)-1-naphthaldehyde



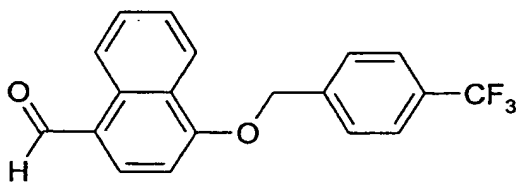
4-allyloxy-1-naphthaldehyde



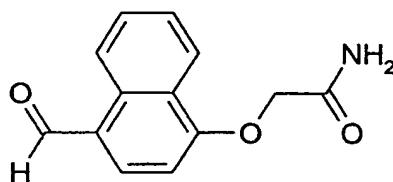
4-(4-trifluoromethoxybenzyloxy)-1-naphthaldehyde



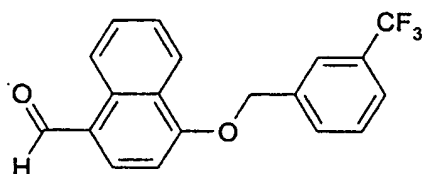
4-propargyloxy-1-naphthaldehyde



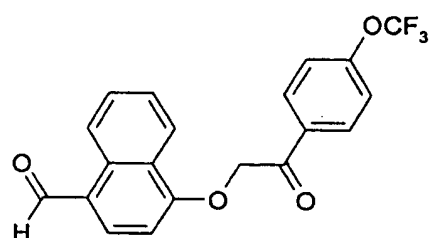
4-(4-trifluoromethylbenzyloxy)-1-naphthaldehyde



2-[(4-carboxaldehyde)-1-naphthyloxy]acetamide  
m.p. 174-175°C

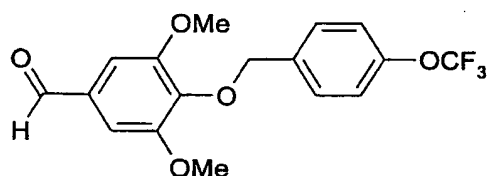


4-(3-trifluoromethylbenzyloxy)-1-naphthaldehyde

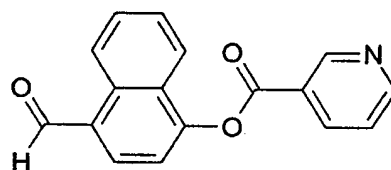


4-(2-(4-trifluoromethoxyphenyl)-2-oxoethoxy)-1-naphthaldehyde

m.p. 112-114°C

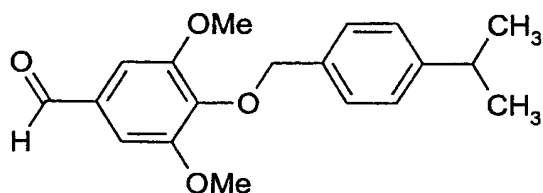


4-(4-trifluoromethoxybenzyloxy)-3,5-dimethoxybenzaldehyde



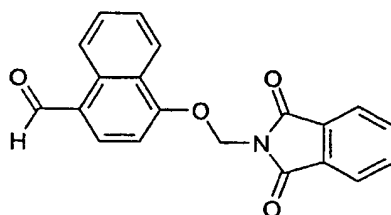
Nicotinic acid 4-formyl-1-naphthyl ester

m.p. 142-143°C



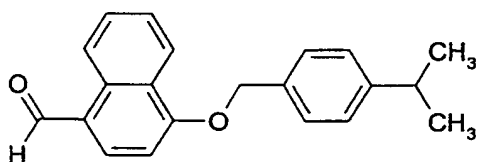
4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzaldehyde

(oil)

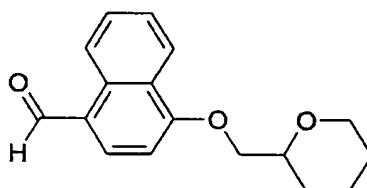


4-(1,3-dioxo-1,3-dihydroisindol-2-ylmethoxy)-1-naphthaldehyde

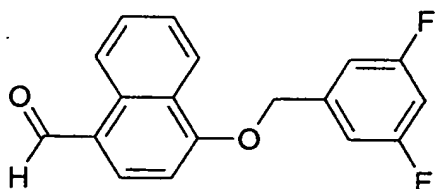
m.p. 191-192°C



4-(4-isopropylbenzyloxy)-1-naphthaldehyde

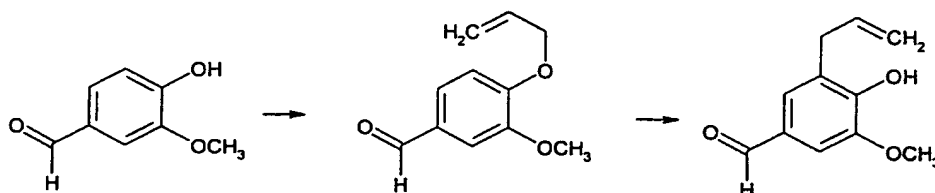


4-(tetrahydro-2-pyranylmethoxy)-1-naphthaldehyde



4-(3,5-difluorobenzoyloxy)-1-naphthaldehyde

m.p. 100-101°C

Preparation of 3-Allyl-4-hydroxy-5-methoxy-benzaldehyde:

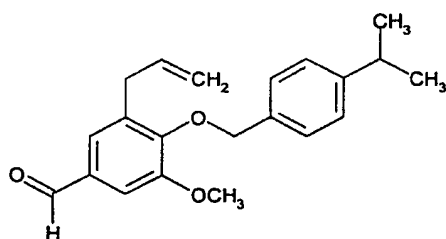
- 5 To a solution of vanillin (1.0 g, 6.57 mmol) in acetone (30 mL) was added potassium carbonate (4.50 g, 32.8 mmol) and allyl bromide (0.62 mL, 7.3 mmol). The mixture was heated under reflux for 6 h. TLC showed appearance of a new spot. Potassium salts were removed by filtration and the filtrate was concentrated to a syrup. A small sample was purified using prep
- TLC using hexane/ethyl acetate 7:3 as developing solvent.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 3.94 (s, 3H), 4.67 - 4.83 (m, 2H), 5.30 - 5.55 (m, 2H), 6.01 - 6.21 (m, 1H), 6.98 (d,  $J$  = 9 Hz, 1H), 7.40 - 7.56 (m, 2H), 9.85 (s, 1H); MS (APCI): 193.6
- 10

- The crude syrup was heated neat in an oil bath at 200 °C for 6 h. The crude material was dissolved in chloroform and filtered through a pack of silica gel. The crude product (yield
- 15 72%) was used as is in the next step for O-alkylation. A small portion was purified using prep-TLC to give a pure sample of 3-allyl-4-hydroxy-5-methoxy-benzaldehyde.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 3.46 (d,  $J$  = 6 Hz, 2 H), 3.96 (s, 3H), 5.02 - 5.22 (m, 2H), 5.94 - 6.11 (m, 1H), 6.30 (s, 1H), 7.45 (s, 2H), 9.80 (s, 1 H); MS (APCI): 193.3.

Preparation of 3-Allyl-4-(4-isopropylbenzyloxy)-5-methoxybenzaldehyde:

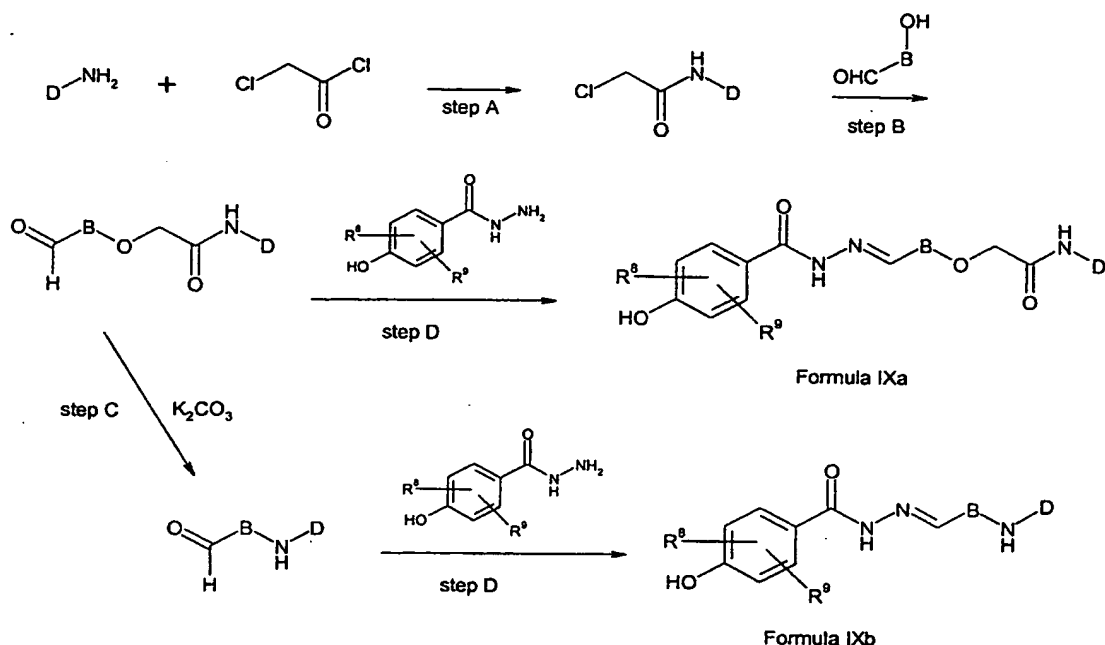
The crude 3-allyl-4-hydroxy-5-methoxy-benzaldehyde was taken up in acetone and treated with 4-isopropylbenzyl chloride in the presence of potassium carbonate to give the desired product.

5



$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.26 (d,  $J$  = 7 Hz, 6 H), 2.92 (m, 1H), 3.38 (d,  $J$  = 7 Hz, 2H), 3.95 (s, 3H), 4.98 - 5.12 (m, 4H), 5.93 - 5.75 (m, 1H), 7.20 - 7.43 (m, 6H), 9.87 (s, 1H).

General procedure for the synthesis of compounds of formulae IXa and IXb:



In the above formulae B, D,  $\text{R}^8$  and  $\text{R}^9$  have the same meanings as defined for formula I.

5 Step A:

To a solution of aniline (or an aniline derivative) (1 eq.) in THF was added dropwise chloroacetyl chloride (1.2 eq.). After stirring at room temperature overnight, 100 mL water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed twice with dilute hydrochloric acid, twice with water, dried over  $\text{MgSO}_4$  and then concentrated to give pure product.

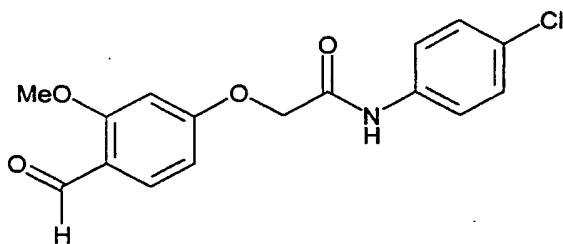
Step B:

To a solution of chloroacetanilide (or a derivative thereof) (1.2 eq.) and 2-methoxy-4-hydroxy benzaldehyde (or another aromatic aldehyde substituted with a hydroxy group) (1 eq.) in DMSO was added potassium carbonate (1.5 eq.). After stirring overnight at room temperature, 100 ml water was added. The mixture was extracted with ethyl acetate, the organic extracts were washed twice with a satd. sodium bicarbonate solution, twice with water, and dried over  $\text{MgSO}_4$ . After concentration in vacuo, the product was obtained.

The following two aldehydes were prepared as examples of compounds that can be prepared using this methodology:

N-(4-Chlorophenyl)-2-(4-formyl-3-methoxyphenoxy)acetamide:

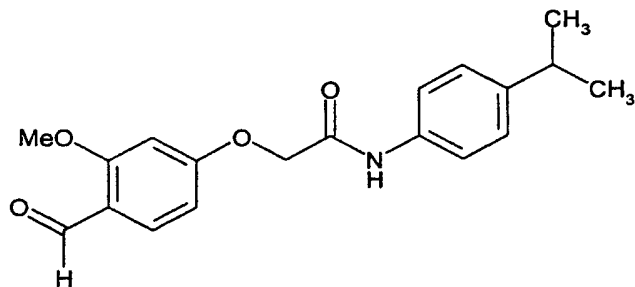
5



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.28 (s, 3H), 5.01 (s, 2H), 6.90 (d, J = 2.2 Hz, 1H), 6.97 (dd, J = 8.6, 2.1 Hz, 1H), 7.67 (d, J = 8.9 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.6 Hz, 1H), 8.51 (s, 1H), 10.66 (s, 1H); MS (APCI): 319.9.

10

N-(4-isopropylphenyl)-2-(4-formyl-3-methoxyphenoxy)acetamide:



15

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.07 (d, J = 6.9 Hz, 6H), 2.70 (m, J = 6.9 Hz, 1H), 3.77 (s, 3H), 4.68 (s, 2H), 6.56 (dd, J = 8.7, 2.1 Hz, 1H), 6.66 (d, J = 2.1 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.7 Hz, 1H), 9.93 (s, 1H), 10.05 (s, 1H); MS (APCI): 328.

20 This type of aldehydes can be coupled to hydrazides using the methodology as described in step D to give a compound of formula IXa. Alternatively these compounds can undergo rearrangement by treatment with base as described below (step C), followed by coupling to a hydrazide (step D) to give a compound of formula IXb.

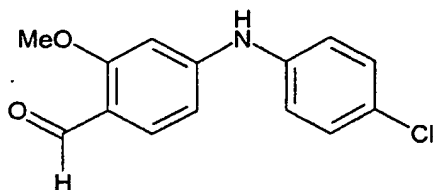
**Step C:**

The mixture of aldehyde (1 eq.) and potassium carbonate (1.5 eq.) in acetonitrile was refluxed. The reaction was monitored by TLC (hexane : ethyl acetate = 2:1). When TLC  
5 showed almost complete conversion (about 48 h), 100 ml water was added. The mixture was extracted with ethyl acetate, the organic extracts were dried over  $\text{MgSO}_4$ , and concentrated to give the desired product which can be further purified by column chromatography, or used directly for the next step.

- 10 The following two aldehydes were prepared as examples of compounds that can be prepared using this methodology:

4-(4-Chlorophenylamino)-2-methoxybenzaldehyde:

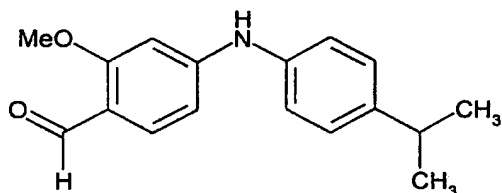
- 15 Prepared from N-(4-chlorophenyl)-2-(4-formyl-3-methoxyphenoxy)acetamide using the procedure described in step C above.



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.84 (s, 3 H), 6.14 (s, 1H), 6.45 (d, J = 2.0 Hz, 1H), 6.54 (dd, J = 8.4, 1.8Hz, 1H), 7.14 (d, J = 8.7Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.5Hz, 1H), 10.22 (s, 1H); MS (APCI): 261.9.

4-(4-isopropylphenylamino)-2-methoxybenzaldehyde:

Prepared from N-(4-isopropylphenyl)-2-(4-formyl-3-methoxyphenoxy)acetamide using the procedure described in step C above.



<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (d, J = 6.9Hz, 6H), 2.88 (m, J = 6.9Hz, 1H), 3.84 (s, 3H), 6.50 (d, J = 1.9Hz, 1H), 6.55 (dd, J = 8.6, 1.8Hz, 1H), 6.96 (s, 1H), 7.15 (d, 2H, J = 8.5Hz, 2H), 7.22 (d, J = 8.5Hz, 2H), 7.69 (d, J = 8.5Hz, 1H), 10.18 (s, 1H); MS (APCI): 269.

Step D:

The resulting carbonyl compounds are treated with the corresponding acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, tert-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N<sub>2</sub> or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction sol-

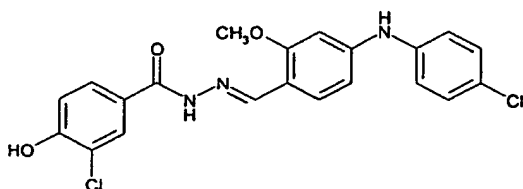
vents. The product can also be isolated by concentration of the reaction mixture *in vacuo*, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate to give a compound of formula IXb.

5

The following compounds of formulae IXa or IXb according to the invention were prepared as examples of compounds that can be prepared using this methodology:

## EXAMPLE 1:

10 3-Chloro-4-hydroxybenzoic acid [4-(4-chlorophenylamino)-2-methoxybenzylidene]hydrazide

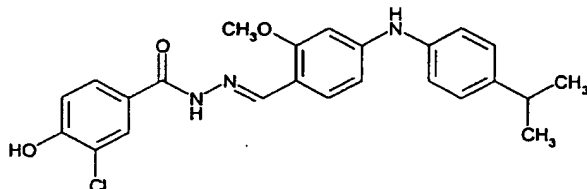


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.81 (s, 3H), 6.72-6.67 (m, 2H), 7.04 (d, J = 8.5Hz, 1H), 7.17 (d, J = 8.7Hz, 2H) 7.31 (d, J = 8.7Hz, 2H), 7.77- 7.70 (m, 2H), 7.96 (d, J = 1.6Hz, 1H), 8.65 (s, 1H), 8.70 (s, 1H), 10.87 (s, 1H), 11.51 (s, 1H); MS (APCI ): 430.

15

## EXAMPLE 2:

20 3-Chloro-4-hydroxybenzoic acid [4-(4-isopropylphenylamino)-2-methoxybenzylidene]hydrazide

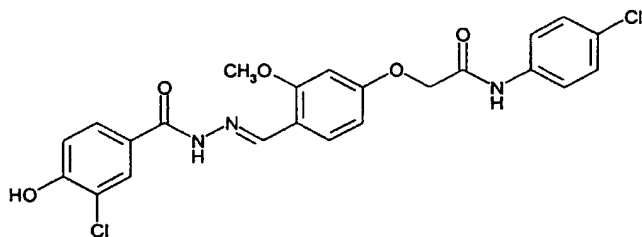


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.18 (2s, 6H), 2.86 (m, 1H), 3.79 (s, 3H), 6.65 (m, 2H), 7.03 (d, 1H), 7.11 (d, 2H), 7.19 (d, 2H), 7.70 (d, 1H), 7.75 (dd, 1H), 7.97 (s, 1H), 8.49 (s, 1H), 8.64 (s, 1H), 10.88 (s, 1H), 11.48 (s, 1H); MS (FAB): 438.16.

25

## EXAMPLE 3:

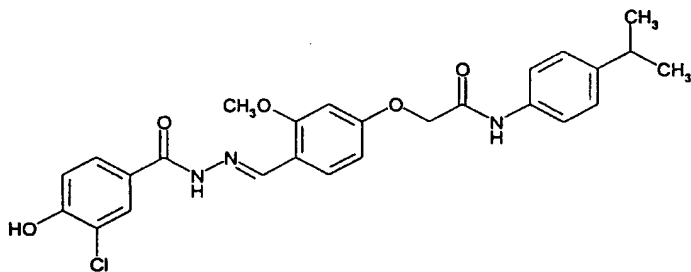
2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenoxy}-N-(4-chlorophenyl)acetamide



$^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  3.66 (s, 3H), 4.57 (s, 2H), 6.48 (d, 1H), 6.55 (s, 1H), 6.83 (d, 1H), 7.20 (d, 2H), 7.48 (d, 2H), 7.56 (dd, 1H), 7.58 (d, 1H), 7.77 (d, 1H), 8.48 (s, 1H), 10.05 (s, 1H), 10.72 (brd s, 1H), 11.40 (s, 1H); MS (APCI): 487.8.

## EXAMPLE 4:

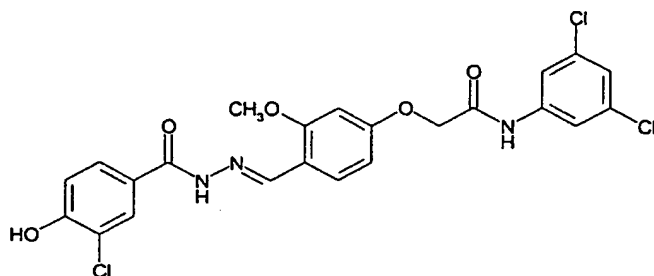
2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenoxy}-N-(4-isopropylphenyl)acetamide



$^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.17 (2 s, 6H), 2.85 (m, 1H), 3.87 (s, 3H), 4.76 (s, 2H), 6.70 (d, 1H), 6.76 (d, 1H), 7.05 (d, 1H), 7.20 (d, 2H), 7.55 (d, 2H), 7.77 (dd, 1H), 7.80 (d, 1H), 7.98 (s, 1H), 8.70 (s, 1H), 10.03 (s, 1H), 10.92 (s, 1H), 11.62 (s, 1H); MS (FAB): 496.16.

## EXAMPLE 5:

2-(4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenoxy)-N-(3,5-dichlorophenyl)acetamide

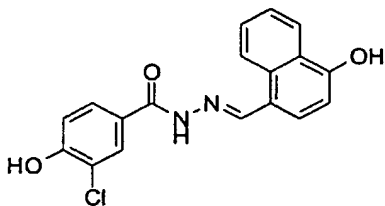


- 5  $^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  4.06 (s, 3H), 4.94 (s, 2H), 6.8 (d, 1H), 6.88 (s, 1H), 7.20 (d, 1H), 7.45 (s, 1H), 7.90 (m, 3H), 8.10 (s, 1H), 8.82 (s, 1H), 10.62 (s, 1H), 11.07 (brd s, 1H), 11.75 (s, 1H); MS (APCI): 524.8.

10 General procedure for the synthesis of alkylidene hydrazides of formula II according to the invention:

- The acylhydrazides are treated with the corresponding carbonyl compounds, such as aldehydes or ketones, in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of  $\text{N}_2$  or Ar at temperatures between  $0^\circ\text{C}$  to  $140^\circ\text{C}$ , preferably between  $10^\circ\text{C}$  to  $80^\circ\text{C}$ . In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/-methanol or dichloromethane/methanol or chloroform/ethyl acetate. The product is isolated by concentration in vacuo of the appropriate fractions. Specific examples illustrating the preparation of compounds according to the invention are provided below.

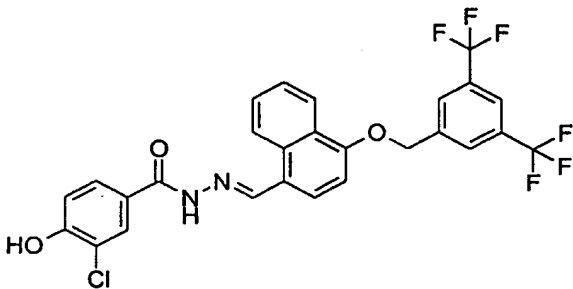
## EXAMPLE 6:

3-Chloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

To a solution of 3-chloro-4-hydroxybenzoic acid hydrazide (200 mg, 1.1 mmol) in DMSO (2 ml) was added 4-hydroxynaphthaldehyde and a catalytic amount of glacial acetic acid (5 drops). The reaction was stirred overnight under nitrogen and diluted with ethyl acetate. The solution was washed with saturated sodium bicarbonate, water, brine, and dried over  $\text{MgSO}_4$ . The organic volume was concentrated *in vacuo* to give the crude product. The product was purified by silica gel column chromatography using  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as the mobile phase.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  6.89 (d, 2H), 7.02 (d, 1H), 7.47 (t, 1H), 7.58 (t, 1H), 7.66 (d, 1H), 7.73 (d, 1H), 7.93 (s, 1H), 8.17 (d, 1H), 8.84 (s, 1H), 8.88 (d, 1H), 10.73 (s, 1H), 10.88 (s, 1H), 11.54 (s, 1H); MS (ESI):  $m/z$  341.04 ( $\text{M}+\text{H}$ ) $^+$ .

## EXAMPLE 7:

3-chloro-4-hydroxybenzoic acid [4-(3,5-bis-trifluoromethylbenzyloxy)-1-naphthylmethylene]-hydrazide

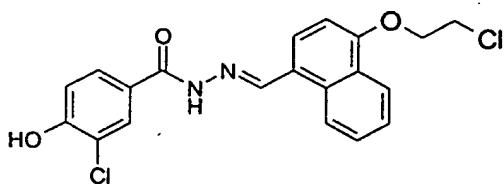
To a solution of 3-chloro-4-hydroxybenzoic acid hydrazide (200 mg, 1.1 mmol) in DMSO (2 mL) was added 4-(3,5-bis-trifluoromethylbenzyloxy)-1-naphthaldehyde (440 mg, 1.1 mmol) and a catalytic amount of glacial acetic acid (5 drops). The reaction was stirred overnight under nitrogen and diluted with ethyl acetate. The solution was washed with saturated sodium bicarbonate, water, brine, and dried over  $\text{MgSO}_4$ . The organic volume was concentrated under

vacuo to give the crude product. The product was purified by silica gel column chromatography using  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as the mobile phase.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  3.77 (s, 6H), 4.91 (s, 2H), 6.95 (s, 2H), 6.99 (d, 1H), 7.30 (d, 2H), 7.52 (d, 2H), 7.68 (m, 1H), 7.89 (s, 1H), 8.29 (s, 1H), 10.90 (broad s, 1H), 11.69 (s, 1H); MS (ESI):  $m/z$  525.37 ( $\text{M}+\text{H}$ ) $^+$ .

#### EXAMPLE 8:

##### 3-chloro-4-hydroxybenzoic acid [4-(2-chloroethoxy)-1-naphthylmethylene]hydrazide



10

A solution of 1-(4-chloroethoxy)naphthaldehyde (2.35 g, 10 mmoles), 3-chloro-4-hydroxy benzoic acid hydrazide (1.87g, 10 mmoles), glacial acetic acid (0.2 mL) and dimethylsulfoxide (DMSO)(15 mL) was stirred at room temperature overnight. Ethyl acetate (100 mL) was added. The solution was extracted with water and brine which induced precipitation. The product (3.1 g, 77% yield) was obtained by suction filtration. The product was purified by recrystallization from ethyl acetate.

15

MS (CI): 235.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  11.5 (s, 1H), 10.7 (s, 1H), 8.7 (bs, 2H), 8.1 (m, 1H), 7.8 (s, 1H), 7.6-7.3 (m, 2H), 7.0 (m, 2H), 4.3 (t, 2H), 3.7 (t, 2H).

By application of the above methodology the following compounds of the invention are synthesized employing the following general procedure:

20

To a solution of 1 mmol of an arylcarboxylic acid hydrazide in 2 ml of anhydrous DMSO was added 1 mmol of the carbonyl compound (an aldehyde or ketone), followed by a catalytic amount of glacial acetic acid. The reaction was stirred overnight under nitrogen and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, water, brine, and dried over  $\text{MgSO}_4$ . Upon partial concentration of the solvent in vacuo, the alkylene

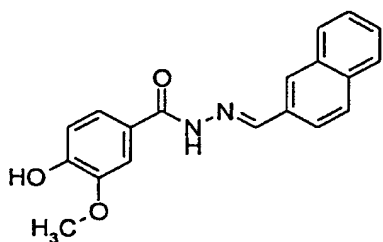
25

hydrazides usually precipitated. The alkylene hydrazides were further purified by recrystallization from

hot ethanol or ethyl acetate, or chromatographed using  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as an eluent.

5 EXAMPLE 9:

4-Hydroxy-3-methoxybenzoic acid (2-naphthylmethylene)hydrazide

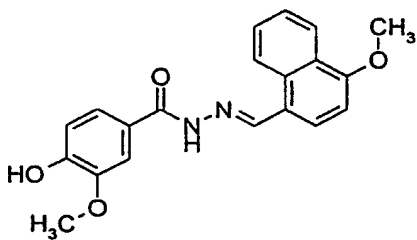


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  3.66 (s, 3 H), 6.67 (d,  $J = 8.2$  Hz, 1 H), 7.32 - 7.47 (m, 5 H), 7.74 (d,  $J = 7.2$  Hz, 1 H), 7.79 (d,  $J = 8.2$  Hz, 2 H), 8.60 (d,  $J = 8.2$  Hz, 1 H), 9.11 (s, 1 H), 11.80 (s, 1 H).

APCI  $m/z$ : 321

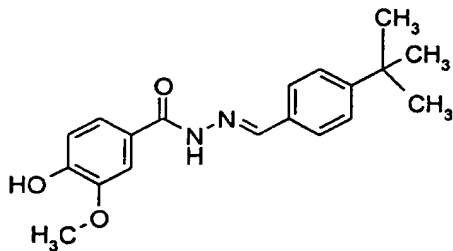
EXAMPLE 10:

15 4-Hydroxy-3-methoxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide



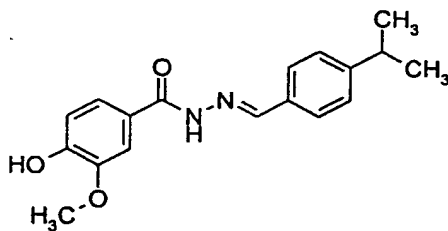
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.80 (s, 3 H), 3.86 (s, 3 H), 6.00 (s, 1 H), 6.59 (d, 1 H), 6.83 (d, 1 H), 7.39 (m, 3 H), 7.52 (s, 1 H), 7.73 (s, 1 H), 8.18 (d, 1 H), 8.58 (d, 1 H), 8.88 (s, 1 H), 9.95 (s, 1 H). MS (APCI): 351.

## EXAMPLE 11:

4-Hydroxy-3-methoxybenzoic acid (4-tert-butylbenzylidene)hydrazide

- 5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 9 H), 3.91 (s, 3 H), 6.16 (s, 1 H), 6.88 (d, 1 H), 7.23 - 7.78 (m, 6 H), 8.28 (s, 1 H), 9.58 (s, 1 H). MS (APCI): 327.

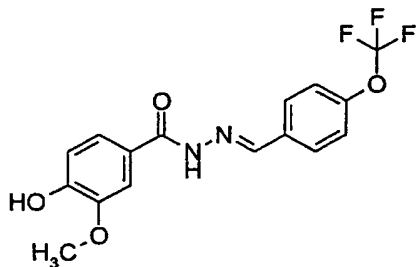
## EXAMPLE 12:

4-Hydroxy-3-methoxybenzoic acid (4-isopropylbenzylidene)hydrazide

10

- $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.29 (d, 6 H), 2.94 (q, 1 H), 3.98 (s, 3 H), 6.13 (s, 1 H), 6.97 (d, 1 H), 7.20 - 7.80 (m, 6 H), 8.29 (s, 1 H), 9.38 (s, 1 H). MS (APCI): 313

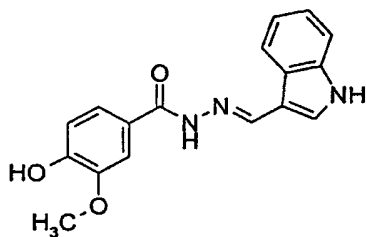
## EXAMPLE 13:

4-Hydroxy-3-methoxybenzoic acid (4-trifluoromethoxybenzylidene)hydrazide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.01 (s, 3 H), 7.04 (d,  $J$  = 8.1 Hz, 1 H), 7.60 - 7.65 (m, 4 H), 8.01 (d,  $J$  = 8.4 Hz, 2 H), 8.63 (s, 1 H), 9.92 (s, 1 H), 11.89 (s, 1 H). MS (APCI): 355, 313, 222, 205.

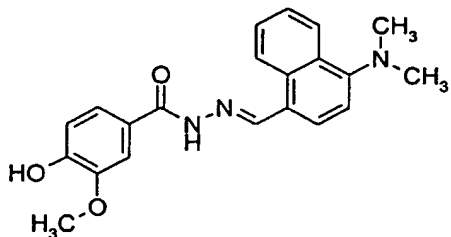
## EXAMPLE 14:

- 10 4-Hydroxy-3-methoxybenzoic acid (1H-indol-3-ylmethylene)hydrazide



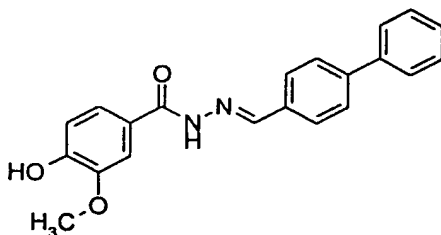
- $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  3.79 (s, 3 H), 6.80 (d,  $J$  = 8.2 Hz, 1 H), 7.11 (m, 2 H), 7.38 (m, 3 H),  
15 7.73 (d,  $J$  = 2.0 Hz, 1 H), 8.53 (d,  $J$  = 7.5 Hz, 1 H), 8.53 (s, 1 H), 9.58 (s, 1 H), 11.23 (s, 1 H), 11.49 (s, 1 H). MS (APCI): 310.

## EXAMPLE 15:

4-Hydroxy-3-methoxybenzoic acid (4-dimethylamino-1-naphthylmethylene)hydrazide

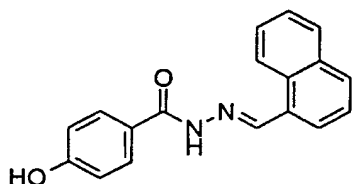
- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.05 (s, 6 H), 4.03 (s, 3 H), 7.06 (d,  $J$  = 8.1 Hz, 1 H), 7.33 (d,  $J$  = 8.0 Hz, 1 H), 7.63 - 7.80 (m, 4 H), 7.97 (d,  $J$  = 8.0 Hz, 1 H), 8.38 (d,  $J$  = 7.9 Hz, 1 H), 9.10 (d,  $J$  = 8.4 Hz, 1 H), 9.15 (s, 1 H), 9.90 (s, 1 H), 11.73 (s, 1 H). MS (APCI): 364.

## EXAMPLE 16:

10 4-Hydroxy-3-methoxybenzoic acid (4-phenylbenzylidene)hydrazide

- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.02 (s, 3 H), 7.04 (d,  $J$  = 8.2 Hz, 1 H), 7.63 - 7.68 (m, 5 H), 7.88 - 7.96 (m, 6 H), 8.64 (s, 1 H), 9.91 (s, 1 H), 11.83 (s, 1 H). MS (APCI): 347.

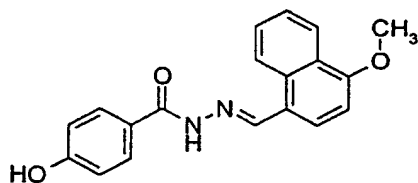
## EXAMPLE 17:

4-Hydroxybenzoic acid (1-naphthylmethylene)hydrazide

5

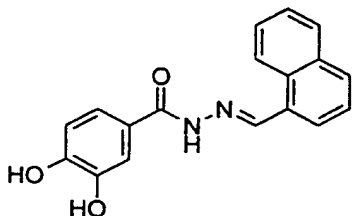
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.82 (d,  $J$  = 8.2 Hz, 2 H), 7.48 - 7.68 (m, 3 H), 7.72 - 7.88 (m, 3 H), 7.95 (d,  $J$  = 8.2 Hz, 2 H), 8.80 (d, 1 H), 9.04 (s, 1 H), 10.14 (s, 1 H). MS (APCI): 291.

## EXAMPLE 18:

10 4-Hydroxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide

15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.97 (s, 3 H), 6.82 (d,  $J$  = 8.6 Hz, 2 H), 7.04 (d,  $J$  = 8.2 Hz, 1 H), 7.52 (dd,  $J$  = 7.3, 7.7 Hz, 1 H), 7.62 (dd,  $J$  = 6.8, 7.7 Hz, 1 H), 7.77 (d,  $J$  = 8.5 Hz, 3 H), 8.19 (d,  $J$  = 8.2 Hz, 1 H), 8.89 (m, 2 H), 10.06 (s, 1 H). MS (APCI): 321.

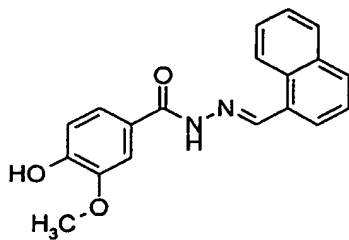
## EXAMPLE 19:

3,4-Dihydroxybenzoic acid (1-naphthylmethylene)hydrazide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.64 (d,  $J$  = 8.6 Hz, 1 H), 7.13 (d,  $J$  = 8.2 Hz, 1 H), 7.19 (d,  $J$  = 2.0 Hz, 1 H), 7.36 - 7.42 (m, 3 H), 7.68 (d,  $J$  = 8.2 Hz, 1 H), 7.80 (d,  $J$  = 8.2 Hz, 2 H), 8.65 (d,  $J$  = 8.2 Hz, 1 H), 8.88 (s, 1 H), 9.07 (s, 1 H), 9.46 (s, 1H), 11.45 (s, 1 H). MS (APCI): 307.

## EXAMPLE 20:

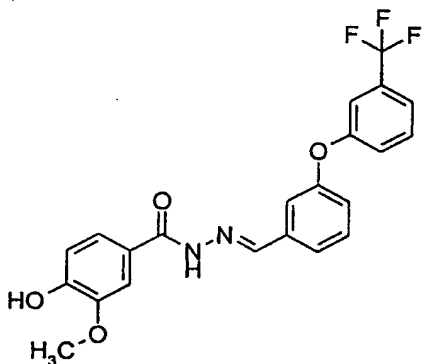
- 10 4-Hydroxy-3-methoxybenzoic acid (1-naphthylmethylene)hydrazide



- $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  3.94 (s, 3H), 6.74 (d, 1H), 7.37-7.52 (m, 6H), 7.77 (d, 1H), 7.89 (d, 2H), 8.67 (d, 1H), 9.93 (s, 1H), 10.90 (s, 1H). MS (APCI): 321.

## EXAMPLE 21:

4-Hydroxy-3-methoxybenzoic acid [3-(3-trifluoromethylphenoxy)benzylidene]hydrazide

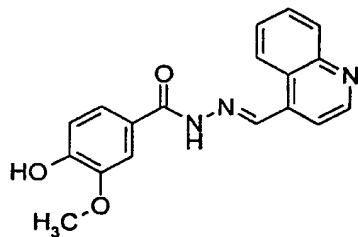


- 5  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  3.83 (s, 3H), 6.85 (d, 1H), 7.16 (dd, 1H), 7.36 (m, 5H), 7.44 (m, 3H), 7.61 (t, 1H), 8.43 (s, 1H), 1.75 (s, 1H), 11.69 (s, 1H). MS (APCI): 431.

## EXAMPLE 22:

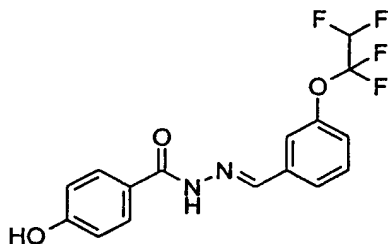
4-Hydroxy-3-methoxybenzoic acid (4-quinolinylmethylene)hydrazide

10



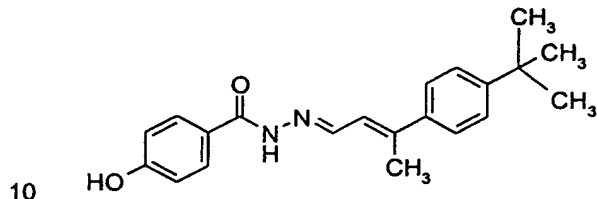
- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.58 (s, 3 H), 6.52 (d,  $J = 8.0$  Hz, 1 H), 7.28 (d,  $J = 7.8$  Hz, 2 H), 7.47 (dd,  $J = J' = 8.1$  Hz, 1 H), 7.59 (m, 2 H), 7.86 (d,  $J = 8.4$  Hz, 1 H), 8.50 (d,  $J = 8.4$  Hz, 1 H),  
15 8.73 (d,  $J = 4.5$  Hz, 1 H), 8.94 (s, 1 H). MS (APCI): 322.

## EXAMPLE 23:

4-Hydroxybenzoic acid [3-(1,1,2,2-tetrafluoroethoxy)benzylidene]hydrazide

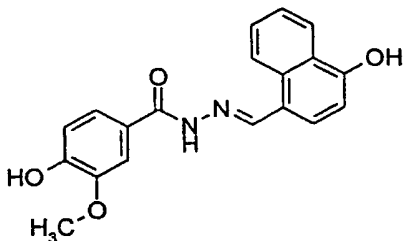
- 5  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  6.49-6.78 (m, 3H), 7.10 (d, 1H), 7.32 (t, 1H), 7.41 (m, 2H), 7.57 (d, 2H), 8.23 (s, 1H), 10.01 (s, 1H), 11.59 (s, 1H). MS (APCI): 357.

## EXAMPLE 24:

4-Hydroxybenzoic acid [3-(4-tert-butylphenyl)but-2-enylidene]hydrazide

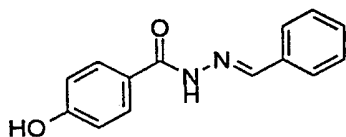
- 10  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.15 (s, 9H), 1.99 (s, 3H), 6.64 (s, 1H), 6.17 (d, 2H), 7.29 (s, 4H), 7.64 (d, 2H), 8.06 (s, 1H), 9.98 (s, 1H), 11.36 (s, 1H). MS (APCI): 337.

## EXAMPLE 25:

4-Hydroxy-3-methoxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.90 (s, 3 H), 6.89 (d, 1 H), 6.99 (d, 1 H), 7.19 (d, 1 H), 7.45 - 7.80 (m, 5 H), 8.22 (d, 1 H), 8.90 (s, 2 H), 9.62 (s, 1 H), 10.68 (s, 1 H). MS (APCI): 337.

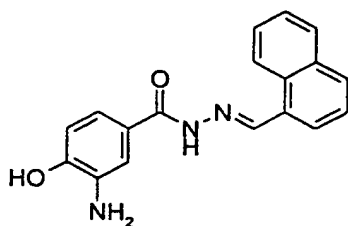
## EXAMPLE 26:

4-Hydroxybenzoic acid (benzylidene)hydrazide

10

- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.86 (d, 2 H), 7.41 - 7.52 (m, 3 H), 7.72 (m, 2 H), 7.82 (d, 2 H), 8.41 (s, 1 H), 10.14 (s, 1 H). MS (APCI): 241.

## EXAMPLE 27:

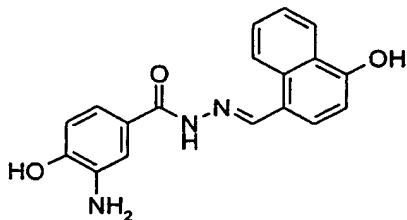
3-Amino-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide

5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.71 (bs, 2 H), 6.68 (d,  $J$  = 8.1 Hz, 1 H), 7.01 (dd,  $J$  = 2.0, 8.2 Hz, 1 H), 7.17 (d,  $J$  = 2.0 Hz, 1 H), 7.51 - 7.62 (m, 3 H), 7.84 (d,  $J$  = 7.2 Hz, 1 H), 7.94 (d,  $J$  = 8.0 Hz, 2 H), 8.75 (d,  $J$  = 7.6 Hz, 1 H), 9.01 (s, 1 H), 9.70 (s, 1 H), 11.54 (s, 1 H). MS (APCI): 306.

10

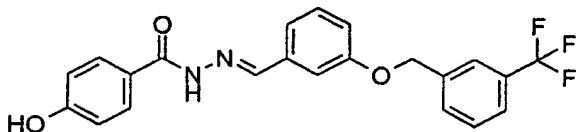
## EXAMPLE 28:

3-Amino-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

15

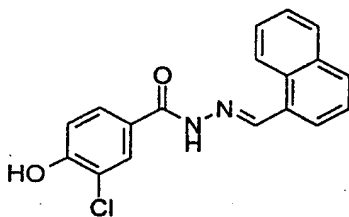
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.68 (bs, 2 H), 6.67 (d,  $J$  = 8.2 Hz, 1 H), 6.91 (d,  $J$  = 7.3 Hz, 1 H), 7.03 (d,  $J$  = 8.2 Hz, 1 H), 7.15 (s, 1 H), 7.43 - 7.65 (m, 3 H), 8.16 (d,  $J$  = 8.2 Hz, 1 H), 8.83 (m, 2 H), 10.71 (s, 1 H), 11.34 (s, 1 H). MS (APCI): 322.

## EXAMPLE 29:

4-Hydroxybenzoic acid [3-(3-trifluoromethylbenzyloxy)benzylidene]hydrazide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  5.28 (s, 2 H), 6.88 (d, 2 H), 7.12 (m, 1 H), 7.24 - 7.50 (m, 3 H), 7.55 - 7.92 (m, 6 H), 8.41 (s, 1 H), 10.16 (s, 1 H), 10.86 (s, 1 H). MS (APCI): 415.

## EXAMPLE 30:

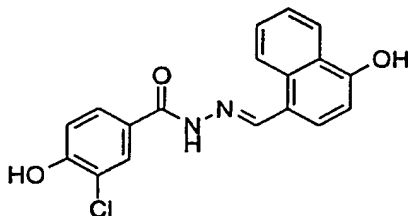
3-Chloro-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide

10

- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.03 (d,  $J$  = 8.2 Hz, 1 H), 7.52 - 7.62 (m, 3 H), 7.74 (d,  $J$  = 8.2 Hz, 1 H), 7.86 (d,  $J$  = 7.0 Hz, 1 H), 7.96 (m, 3 H), 8.79 (d,  $J$  = 8.2 Hz, 1 H), 9.01 (s, 1 H), 10.94 (s, 1 H), 11.76 (s, 1 H). MS (APCI): 325.

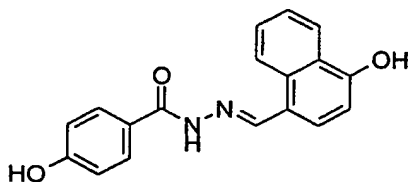
15

## EXAMPLE 31:

3-Chloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

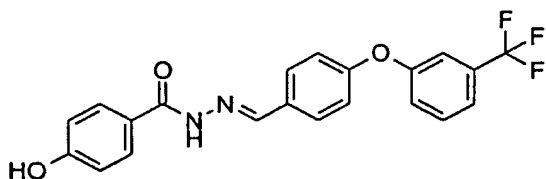
- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.90 (d,  $J$  = 8.0 Hz, 1 H), 7.02 (d,  $J$  = 8.5 Hz, 1 H), 7.50 (dd,  $J$  =  $J'$  = 7.8 Hz, 1 H), 7.58 (dd,  $J$  = 7.1, 8.0 Hz, 1 H), 7.65 (d,  $J$  = 8.0 Hz, 1 H), 7.72 (d,  $J$  = 8.5 Hz, 1 H), 7.93 (s, 1 H), 8.17 (d,  $J$  = 8.2 Hz, 1 H), 8.83 (s, 1 H), 8.88 (d,  $J$  = 8.5 Hz, 1 H), 10.73 (s, 1 H), 10.88 (s, 1 H), 11.54 (s, 1 H). MS (APCI): 343, 341.

## 10 EXAMPLE 32:

4-Hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.88 (d, 2 H), 6.98 (d, 1 H), 7.55 (dd, 1 H), 7.64 (dd, 1 H), 7.71 (d, 1 H), 7.82 (d, 2 H), 8.22 (d, 1 H), 8.94 (m, 2 H), 10.11 (s, 1 H), 10.77 (s, 1 H). MS (APCI): 307.

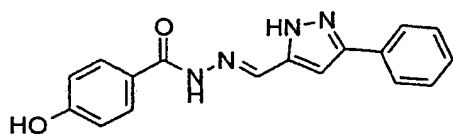
## EXAMPLE 33:

4-Hydroxybenzoic acid [4-(3-trifluoromethylphenoxy)benzylidene]hydrazide

5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.81(d, 2 H), 6.98 (d, 1 H), 7.13 (dd, 1 H), 7.30 - 7.48 (m, 3 H), 7.48 - 7.60 (m, 3 H), 7.68 (dd, 1 H), 7.81 (d, 2 H), 8.41 (s, 1 H). MS (APCI): 401.

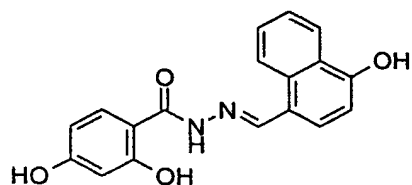
## EXAMPLE 34:

10 4-Hydroxybenzoic acid (5-phenyl-3-pyrazolylmethylene)hydrazide

15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.81 (d, 2 H), 7.40 - 7.62 (m, 5 H), 7.78 (d, 2 H), 8.09 (s, 1 H), 8.50 (s, 1 H). MS (APCI): 307.

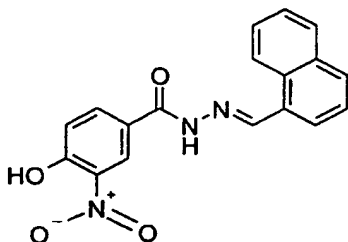
## EXAMPLE 35:

2,4-Dihydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

20

$^1\text{H}$  NMR (DMSO- $d_6$ ): 6.35 (s, 1 H), 6.39 (d, 1 H), 6.99 (d, 1 H), 7.51 (dd, 1 H), 7.65 (dd, 1 H), 7.73 (d, 1 H), 7.82 (d, 1 H), 8.26 (d, 1 H), 8.88 (s, 1 H), 8.98 (d, 1 H), 10.0 - 11.0 (m, 4 H). MS (APCI): 323.

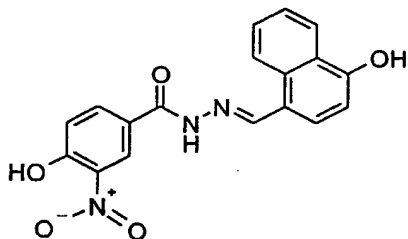
## EXAMPLE 36:

4-Hydroxy-3-nitrobenzoic acid (1-naphthylmethylene)hydrazide

5

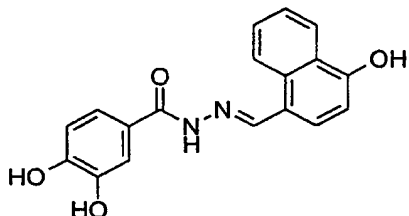
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.15 (d,  $J$  = 9.3 Hz, 1 H), 7.37 - 7.48 (m, 4 H), 6.70 (d,  $J$  = 7.1 Hz, 1 H), 7.78 - 7.82 (m, 2 H), 8.29 (s, 1 H), 8.43 (d,  $J$  = 8.5 Hz, 1 H), 8.85 (s, 1 H).

## EXAMPLE 37:

10 4-Hydroxy-3-nitrobenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

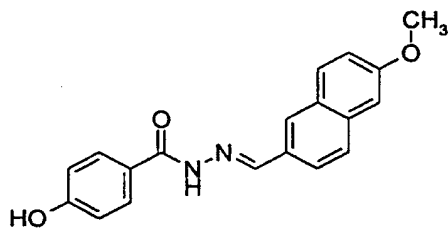
15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.24 (d,  $J$  = 9.3 Hz, 1 H), 6.83 (d,  $J$  = 8.0 Hz, 1 H), 7.37 - 7.52 (m, 3 H), 7.57 (d,  $J$  = 8.0 Hz, 1 H), 8.10 (d,  $J$  = 8.0 Hz, 1 H), 8.34 (s, 1 H), 8.76 (s, 1 H), 8.79 (s, 1 H), 10.57 (s, 1 H), 11.17 (m, 1 H).

## EXAMPLE 38:

3,4-Dihydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

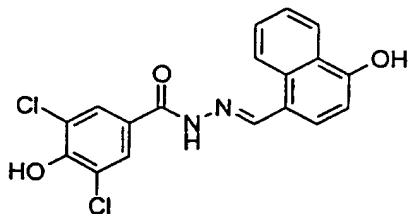
- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.86 (d, 1 H), 6.98 (d, 1 H), 7.32 (d, 1 H), 7.42 (s, 1H), 7.56 (dd, 1 H), 7.63 (dd, 1 H), 7.71 (d, 1 H), 8.24 (d, 1 H), 8.88 (s, 1 H), 8.92 (m, 2 H), 9.26 (s, 1 H), 9.54 (s, 1 H), 10.75 (s, 1 H). MS (APCI): 323.

## EXAMPLE 39:

10 4-Hydroxybenzoic acid (6-methoxy-2-naphthylmethylene)hydrazide

- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.89 (s, 3 H), 6.86 (d,  $J$  = 8.6 Hz, 2 H), 7.22 (dd,  $J$  = 2.3, 8.9 Hz, 1 H), 7.37 (d,  $J$  = 2.3 Hz, 1 H), 7.80 - 7.93 (m, 6 H), 8.04 (s, 1 H), 8.53 (s, 1 H), 11.67 (s, 1 H).  
15 MS (APCI): 321.

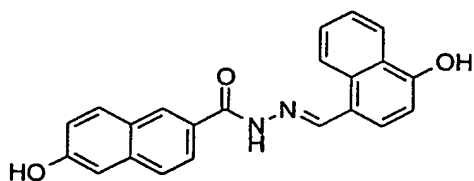
## EXAMPLE 40:

3,5-Dichloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.98 (d, 1 H), 7.58 (dd, 1 H), 7.68 (dd, 1 H), 7.78 (d, 1 H), 8.02 (s, 2 H), 8.27 (d, 1 H), 8.90 (s, 1 H), 8.96 (d, 1 H), 10.81 (s, 1 H), 10.98 (s, 1 H), 11.67 (s, 1 H).  
MS (APCI): 375, 377.

## EXAMPLE 41:

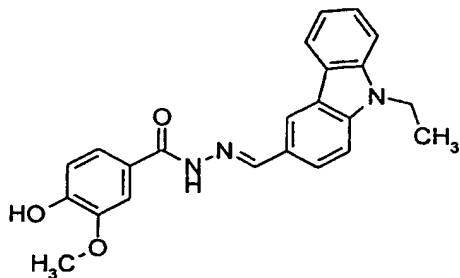
10 6-Hydroxy-2-naphthoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.04 (d, 2 H), 6.33 (m, 1 H), 6.62 (dd, 2 H), 6.79 (dd, 2 H), 7.06 (d, 2 H), 7.44 (d, 2 H), 8.27 (d, 2 H), 8.39 (s, 2 H).

15

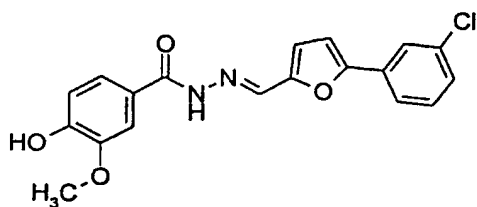
## EXAMPLE 42:

4-Hydroxy-3-methoxybenzoic acid (9-ethyl-9H-3-carbazolylmethylene)hydrazide

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.34 (t, J = 7.0 Hz, 3 H), 3.88 (s, 3 H), 4.47 (q, J = 7.0 Hz, 2 H), 6.90 (d, J = 8.0 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.47 - 7.54 (m, 3 H), 7.64 (d, J = 8.2 Hz, 1 H), 7.69 (d, J = 8.5 Hz, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 8.24 (d, J = 7.7 Hz, 1 H), 8.45 (s, 1 H),  
5 8.62 (s, 1 H) 9.62 (s, 1 H), 11.51 (s, 1H). MS (APCI): 388.

## EXAMPLE 43:

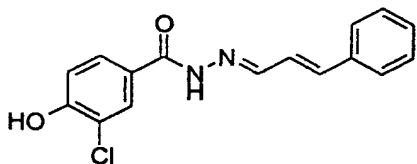
4-Hydroxy-3-methoxybenzoic acid [5-(3-chlorophenyl)-2-furanylmethylene]hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.93 (s, 3 H), 6.97 (d, J = 8.2 Hz, 1 H), 7.14 (d, J = 3.5 Hz, 1 H), 7.37 (d, J = 3.5 Hz, 1 H), 7.48 - 7.63 (m, 4 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.93 (s, 1 H), 8.47 (s, 1 H), 9.85 (s, 1 H), 11.75 (s, 1 H). MS (APCI): 371.

## EXAMPLE 44:

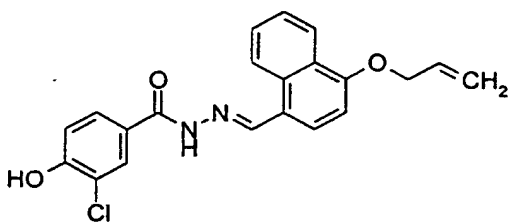
3-Chloro-4-hydroxybenzoic acid (3-phenylallylidene)hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.00 (m, 3 H), 7.22 - 7.40 (m, 3 H), 7.57 (d, 2 H), 7.69 (d, 1 H), 7.89 (s, 1 H), 8.12 (d, 1 H), 11.0 (s, 1 H), 12.0 (s, 1 H). MS (APCI): 301.

## EXAMPLE 45:

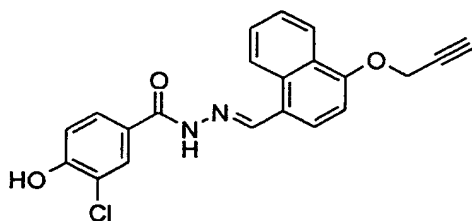
3-Chloro-4-hydroxybenzoic acid (4-allyloxy-1-naphtylmethylene)hydrazide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.68 (m, 2 H), 5.21 (d, 1 H), 5.38 (d, 1 H), 5.90 -6.10 (m, 1 H), 6.86 (dd, 2 H), 7.42 (dd, 1 H), 7.53 (dd, 1 H), 7.67 (dd, 2 H), 7.86 (s, 1 H), 8.18 (d, 1 H), 8.78 (s, 1 H), 8.82 (d, 1 H), 10.9 (s, 1 H), 12.0 (s, 1 H). MS (APCI): 381.

## EXAMPLE 46:

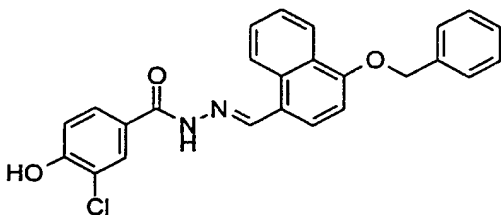
3-Chloro-4-hydroxybenzoic acid (4-ethynylmethoxy-1-naphthylmethylene)hydrazide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.60 (s, 1 H), 5.06 (s, 2 H), 6.99 (d, 1 H), 7.12 (d, 1 H), 7.55 (t, 1 H), 7.66 (t, 1 H), 7.73 (t, 1 H), 7.93 (s, 1 H), 8.02 (d, 1 H), 8.16 (t, 1 H), 8.86 (d, 1 H), 9.27 (d, 1 H), 10.90 (s, 1 H), 11.62 (s, 1 H). MS (APCI): 378.

## EXAMPLE 47:

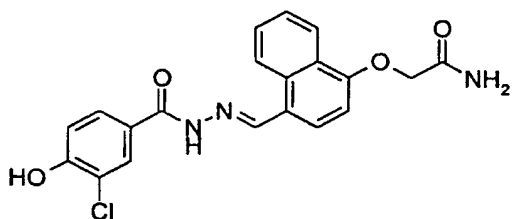
3-Chloro-4-hydroxybenzoic acid (4-benzyloxy-1-naphthylmethylene)hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.40 (s, 2 H), 7.08 (d, 1 H), 7.08 (s, 1 H), 7.39 (d, 1 H), 7.43 (m, 3 H), 7.70 (m, 5 H), 8.00 (s, 1 H), 8.01 (d, 1 H), 8.33 (t, 1 H), 8.94 (d, 1 H), 9.35 (d, 1 H), 10.98 (s, 1 H), 11.69 (s, 1 H). MS (APCI): 431, 433.

5 EXAMPLE 48:

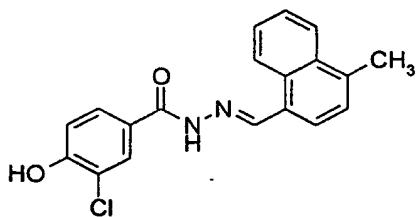
2-(4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyloxy)acetamide



10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.68 (d, 2 H), 6.94 (d, 1 H), 6.98 (dd, 1H), 7.40 - 7.86 (m, 5 H), 8.00 (m, 1 H), 8.48 (dd, 1 H), 8.93 (m, 1 H), 9.38 (m, 1 H). MS (APCI): 398.

EXAMPLE 49:

3-Chloro-4-hydroxybenzoic acid (4-methyl-1-naphthylmethylene)hydrazide

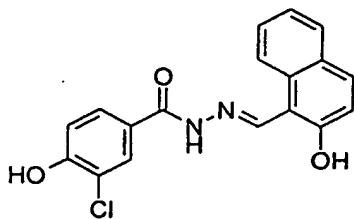


15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.70 (s, 3 H), 7.10 (d, 1 H), 7.49 (d, 1 H), 7.67 (m, 2 H), 7.81 (m, 2 H), 8.00 (s, 1 H), 8.11 (d, 1 H), 8.88 (d, 1 H), 9.07 (s, 1H), 11.0 (s, 1 H). MS (APCI): 339, 341.

20

EXAMPLE 50:

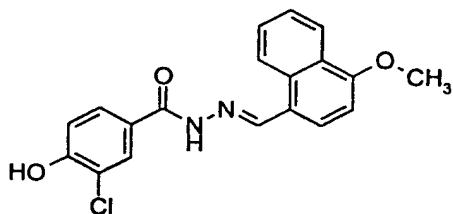
3-Chloro-4-hydroxybenzoic acid (2-hydroxy-1-naphthylmethylene)hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.98 (d, 1 H), 7.98 (d, 1 H), 7.29 (dd, 1 H), 7.48 (dd, 1 H), 7.69 (d, 1 H), 7.78 (dd, 2 H), 7.90 (s, 1 H), 8.06 (d, 1 H), 9.32 (s, 1 H), 11.00 (s, 1 H). MS (APCI): 341.

#### EXAMPLE 51:

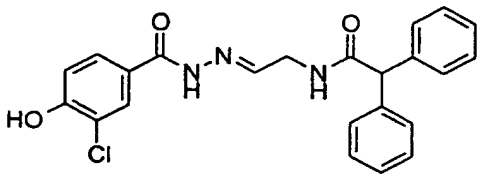
3-Chloro-4-hydroxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazone



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.05 (s, 3 H), 7.06 (m, 2 H), 7.59 (dd, 1 H), 7.70 (dd, 1 H), 7.81 (d, 1 H), 7.86 (d, 1 H), 8.00 (s, 1 H), 8.27 (d, 1 H), 8.93 (s, 1 H), 8.99 (d, 1 H), 11.00 (s, 1 H). MS (APCI): 341, 339.

#### EXAMPLE 52:

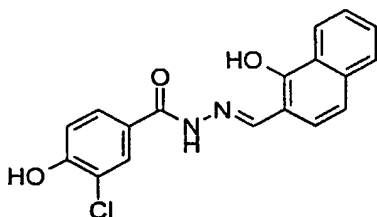
N-(2-[(3-Chloro-4-hydroxybenzoyl)hydrazono]ethyl)-2,2-diphenylacetamide



$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  3.85 (t, 2 H), 4.93 (s, 2 H), 7.16 - 7.25 (m, 10 H), 7.26 (m, 1 H), 7.62 (d, 1 H), 7.82 (s, 1 H), 8.69 (t, 1 H), 10.85 (s, 1 H), 11.39 (s, 1 H). MS (APCI): 422

## EXAMPLE 53:

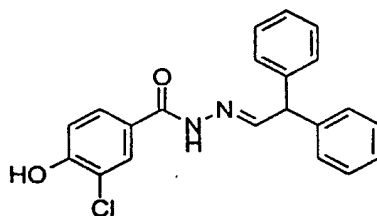
5 3-Chloro-4-hydroxybenzoic acid (1-hydroxy-2-naphthylmethylene)hydrazide



10  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.99 (d, 1 H), 7.22 (d, 1 H), 7.37 - 7.56 (m, 4 H), 7.68 (dd, 1 H), 7.77 (d, 1 H), 7.90 (s, 1 H), 8.19 (d, 1 H), 8.58 (s, 1 H), 11.00 (s, 1 H). MS (APCI): 341.

## EXAMPLE 54:

3-Chloro-4-hydroxybenzoic acid (2,2-diphenylethylidene)hydrazide

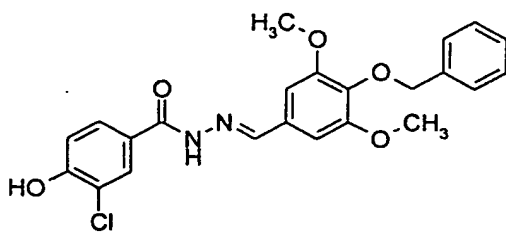


15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.94 (d, 1 H), 6.98 (d, 1 H), 7.11 - 7.22 (m, 5 H), 7.22 - 7.34 (m, 4 H), 7.68 (d, 1 H), 7.82 (s, 1 H), 8.19 (d, 1 H), 11.00 (s, 1 H). MS (APCI): 365, 367.

## EXAMPLE 55:

20 3-Chloro-4-hydroxybenzoic acid (4-benzyloxy-3,5-dimethoxybenzylidene)hydrazide

177

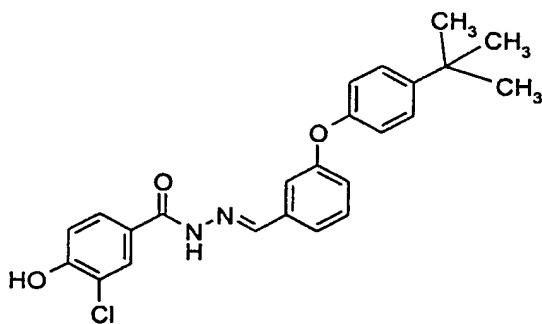


$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.86 (s, 6 H), 4.98 (s, 2 H), 7.03 (s, 2 H), 7.09 (d, 1 H), 7.25 - 7.33 (m, 3 H), 7.48 (m, 2 H), 7.89 (dd, 1 H), 7.99 (s, 1 H), 8.32 (s, 1 H), 11.00 (s, 1 H). MS (APCI): 441.

5

## EXAMPLE 56:

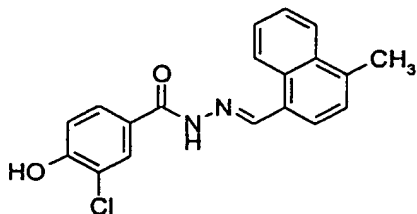
3-Chloro-4-hydroxybenzoic acid [3-(4-tert-butylphenoxy)benzylidene]hydrazide



10  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.05 (s, 9 H), 6.90 (m, 3 H), 7.09 (d, 1 H), 7.30 (t, 1 H), 7.40 (m, 3 H), 7.69 (m, 2 H), 7.88 (s, 1 H), 8.44 (s, 1 H), 10.60 (s, 1 H), 11.55 (s, 1 H). MS (APCI): 423.

## EXAMPLE 57:

3-Chloro-4-hydroxybenzoic acid (4-methyl-1-naphthylmethylene)hydrazide

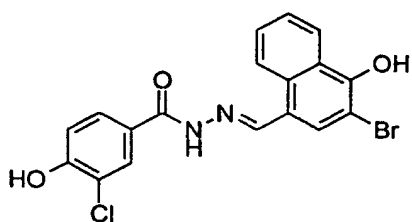


15

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  2.64 (s, 3 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.41 (d,  $J$  = 7.4 Hz, 1 H), 7.58 (m, 2 H), 7.78 (m, 2 H), 7.95 (d,  $J$  = 2.0 Hz, 1 H), 8.06 (dd,  $J$  = 2.0, 8.0 Hz, 1 H), 8.82 (d,  $J$  = 8.0 Hz, 1 H), 9.07 (s, 1 H), 10.93 (s, 1 H), 11.71 (s, 1 H). MS (APCI): 337. 339.

5 EXAMPLE 58:

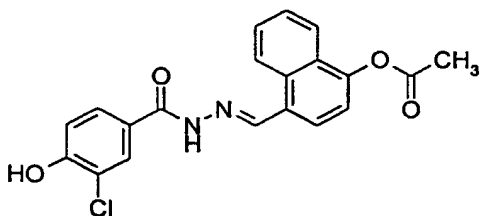
3-Chloro-4-hydroxybenzoic acid (3-bromo-4-hydroxy-1-naphthylmethylene)hydrazide



10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.02 (d,  $J$  = 8.5 Hz, 1 H), 7.51 - 7.62 (m, 4 H), 7.80 (dd,  $J$  = 2.0, 8.5 Hz, 1 H), 8.00 (d,  $J$  = 2.0 Hz, 1 H), 8.21 (s, 1 H), 8.59 (d,  $J$  = 8.5 Hz, 1 H), 8.91 (s, 1 H). MS (APCI): 421, 423.

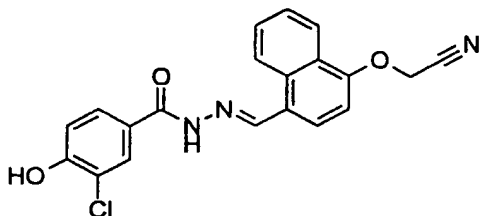
EXAMPLE 59:

15 Acetic acid 4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyl ester



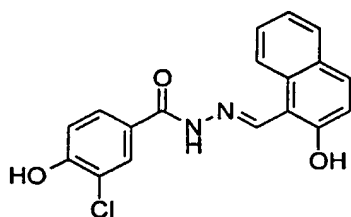
20  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  2.63 (s, 3 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.36 (d,  $J$  = 8.0 Hz, 1 H), 7.60 (dd,  $J$  = 7.0, 7.5 Hz, 1 H), 7.68 (dd,  $J$  = 7.0, 8.0 Hz, 1 H), 7.75 (dd,  $J$  = 1.4, 8.0 Hz, 1 H), 7.89 (d,  $J$  = 8.0 Hz, 1 H), 7.97 (d,  $J$  = 8.0 Hz, 2 H), 8.85 (d,  $J$  = 8.5 Hz, 1 H), 9.08 (s, 1 H), 11.0 (s, 1 H), 11.78 (s, 1 H). MS (APCI): 383.

## EXAMPLE 60:

3-Chloro-4-hydroxybenzoic acid (4-cyanomethoxy-1-naphthylmethylene)hydrazide

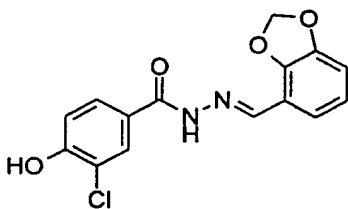
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.40 (s, 2 H), 7.00 (d, 1 H), 7.21 (d, 1 H), 7.58 - 7.80 (m, 3 H), 7.82  
5 (d, 1 H), 7.96 (s, 1 H), 8.18 (d, 1 H), 8.90 (s, 2 H), 9.28 (s, 1 H), 11.62 (s, 1 H). MS (APCI):  
380, 382.

## EXAMPLE 61:

3-Chloro-4-hydroxybenzoic acid (2-hydroxy-1-naphthylmethylene)hydrazide

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.18 (d, 1 H), 7.30 (d, 1 H), 7.50 (dd, 1H), 7.68 (dd, 1 H), 7.88 (d, 1  
H), 7.95 (m, 2 H), 8.08 (s, 1 H), 8.29 (d, 1 H), 9.51 (s, 1 H), 11.12 (s, 1 H), 12.12 (s, 1 H).  
MS (APCI): 341, 343.

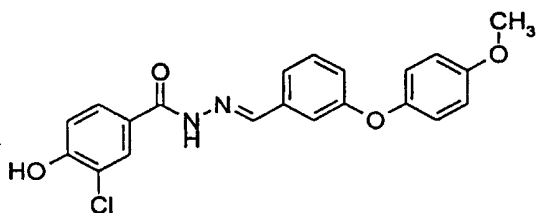
## EXAMPLE 62:

3-Chloro-4-hydroxybenzoic acid (2,3-methylenedioxybenzylidene)hydrazide

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.06 (s, 2 H), 6.86 (dd, 1 H), 6.90 (dd, 1H), 7.01 (d, 1 H), 7.25 (d, 1 H), 7.71 (dd, 1 H), 7.92 (s, 1 H), 8.49 (s, 1 H), 10.93 (s, 1 H), 11.70 (s, 1 H). MS (APCI): 319, 321.

5 EXAMPLE 63:

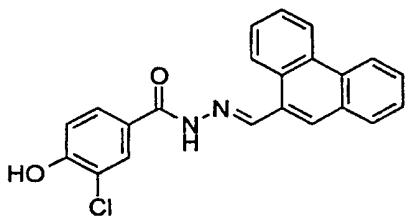
3-Chloro-4-hydroxybenzoic acid [3-(4-methoxyphenoxy)benzylidene]hydrazide



10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.98 (s, 3 H), 7.38 (m, 6 H), 7.48 (s, 1 H), 7.72 (m, 2 H), 7.97 (d, 1 H), 8.19 (s, 1 H), 8.64 (s, 1 H), 11.93 (s, 1 H). MS (APCI): 397, 399.

EXAMPLE 64:

3-Chloro-4-hydroxybenzoic acid (9-phenanthrenylmethylene)hydrazide



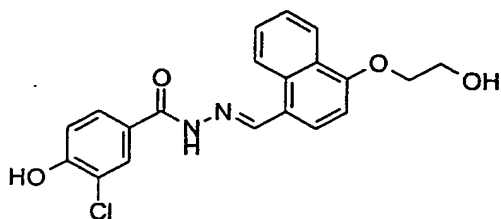
15

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.02 (d, 1 H), 7.52 - 7.83 (m, 5 H), 7.99 (d, 1 H), 8.08 (d, 1 H), 8.21 (s, 1 H), 8.82 (d, 1 H), 8.89 (dd, 1 H), 8.96 (dd, 1 H), 9.06 (s, 1 H), 10.96 (s, 1 H), 11.82 (s, 1 H). MS (APCI): 375, 377.

20

EXAMPLE 65:

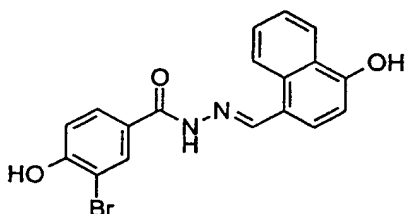
3-Chloro-4-hydroxybenzoic acid [4-(2-hydroxyethoxy)-1-naphthylmethylene]hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.81 (t, J = 4.8 Hz, 2 H), 4.16 (t, J = 4.8 Hz, 2 H), 6.46 (d, J = 8.5 Hz, 1 H), 7.01 (d, J = 8.5 Hz, 1 H), 7.51 - 7.61 (m, 3 H), 7.72 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 2.1 Hz, 1 H), 8.30 (d, J = 8.2 Hz, 1 H), 8.85 (s, 1 H), 8.87 (d, J = 8.5 Hz, 1 H), 11.38 (s, 1 H). MS (APCI): 385, 387.

## EXAMPLE 66:

3-Bromo-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



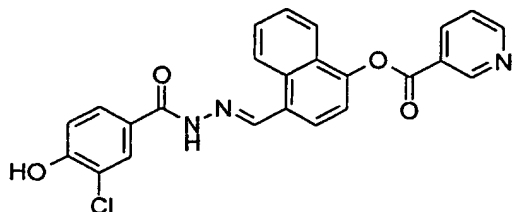
10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.90 (d, J = 8.0 Hz, 1 H), 7.00 (d, J = 8.0 Hz, 1 H), 7.47 (dd, J = J' = 8.0 Hz, 1 H), 7.58 (dd, J = J'' = 8.0 Hz, 1 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.77 (dd, J = 2.0, 8.0 Hz, 1 H), 8.08 (d, J = 2.0 Hz, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 8.83 (s, 1 H), 8.88 (d, J = 8.0 Hz, 1 H), 10.73 (s, 1 H), 11.53 (s, 1 H). MS (APCI): 385, 387.

15

## EXAMPLE 67:

Nicotinic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyl ester

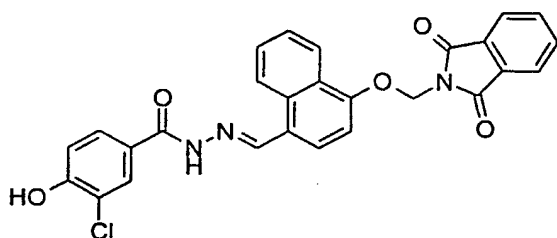


<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.04 (d, J = 8.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.64 - 7.69 (m, 4 H), 7.74 - 8.02 (m, 3 H), 8.56 (dd, J = 2.0, 8.0 Hz, 1 H), 8.91 (m, 2 H), 9.05 (s, 1 H), 8.35 (d, J = 1.8 Hz, 1 H), 10.96 (s, 1 H), 11.84 (s, 1 H). MS (APCI): 446, 448.

5

## EXAMPLE 68:

3-Chloro-4-hydroxybenzoic acid [4-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethoxy)-1-naphthylmethylene]hydrazide



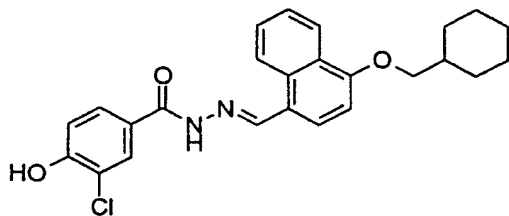
10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.78 (s, 2 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.48 (m, 1 H), 7.61 (m, 1 H), 7.73 - 7.81 (m, 8 H), 8.90 (m, 2 H), 10.91 (s, 1 H), 11.67 (s, 1 H). MS (APCI): 500, 502.

15

## EXAMPLE 69:

3-Chloro-4-hydroxybenzoic acid [4-(cyclohexylmethoxy)-1-naphthylmethylene]hydrazide



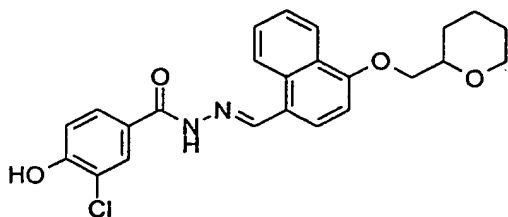
20

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.08 - 1.19 (m, 4 H), 1.66 - 1.72 (m, 3 H), 1.83 - 1.92 (m, 3 H), 3.21 (m, 1 H), 3.95 (m, 2 H), 6.99 (d, J = 8.1 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.53 (dd, J = J'

= 7.4 Hz, 1 H), 7.62 (dd,  $J = J' = 7.5$  Hz, 1 H), 7.72 - 7.93 (m, 2 H), 7.94 (d,  $J = 2.1$  Hz, 1 H), 8.22 (d,  $J = 8.0$  Hz, 1 H), 8.87 (s, 1 H), 8.90 (d,  $J = 8.5$  Hz, 1 H), 10.94 (s, 1 H), 11.60 (s, 1 H). MS (APCI): 437, 439.

5 EXAMPLE 70:

3-Chloro-4-hydroxybenzoic acid [4-(tetrahydro-2-pyranylmethoxy)-1-naphthylmethylene]-hydrazide



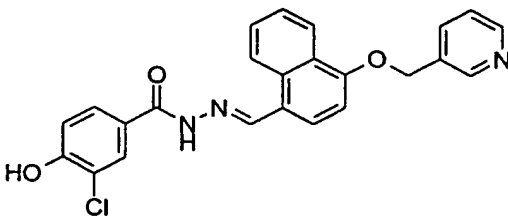
10

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.35 (m, 3 H), 1.60 - 1.71 (m, 2 H), 3.15 - 3.38 (m, 2 H), 3.64 (m, 1 H), 3.78 (m, 1 H), 4.02 (m, 2 H), 6.94 (d,  $J = 8.5$  Hz, 2 H), 7.46 (dd,  $J = J' = 7.4$  Hz, 1 H), 7.54 (dd,  $J = J' = 8.2$  Hz, 1 H), 7.66 (m, 2 H), 7.86 (d,  $J = 2.1$  Hz, 1 H), 8.13 (d,  $J = 8.0$  Hz, 1 H), 8.78 (s, 1 H), 8.83 (d,  $J = 8.5$  Hz, 1 H), 10.83 (s, 1 H), 11.52 (s, 1 H). MS (APCI): 439,

15 441.

EXAMPLE 71:

3-Chloro-4-hydroxybenzoic acid [4-(3-pyridylmethoxy)-1-naphthylmethylene]hydrazide



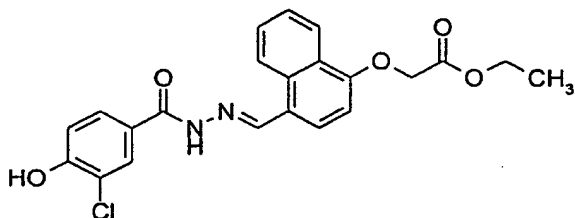
20

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  5.28 (m, 2 H), 6.94 (d,  $J = 8.5$  Hz, 1 H), 7.10 (d,  $J = 8.5$  Hz, 1 H), 7.34 (dd,  $J = 4.8, 7.8$  Hz, 1 H), 7.45 (dd,  $J = J' = 7.6$  Hz, 1 H), 7.54 (dd,  $J = J' = 7.5$  Hz, 1 H), 7.66 (d,  $J = 8.5$  Hz, 1 H), 7.70 (d,  $J = 8.2$  Hz, 1 H), 7.86 (m, 2 H), 8.15 (d,  $J = 8.0$  Hz, 1 H),

8.45 (dd,  $J = 1.5, 4.8$  Hz, 1 H), 8.65 (s, 1 H), 8.81 (m, 2 H), 10.90 (s, 1 H), 11.56 (s, 1 H). MS (APCI): 432, 434.

EXAMPLE 72:

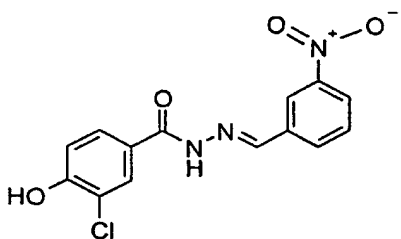
5 4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyloxy)acetic acid ethyl ester



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.25 (t,  $J = 7.0$  Hz, 3 H), 4.25 (q,  $J = 7.0$  Hz, 2 H), 5.11 (s, 2 H), 7.06 (d,  $J = 8.2$  Hz, 1 H), 7.13 (d,  $J = 8.5$  Hz, 1 H), 7.64 -7.70 (m, 2 H), 7.76 (d,  $J = 8.2$  Hz, 2 H),  
10 8.04 (d,  $J = 2.1$  Hz, 1 H), 8.36 (d,  $J = 8.2$  Hz, 1 H), 8.97 (s, 1 H), 9.02 (d,  $J = 8.5$  Hz, 1 H), 11.01 (s, 1 H), 11.74 (s, 1 H). MS (APCI): 427, 429.

EXAMPLE 73:

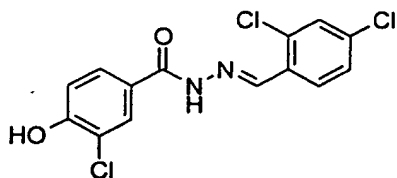
3-Chloro-4-hydroxybenzoic acid (3-nitrobenzylidene)hydrazide



15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.13 (d,  $J = 8.5$  Hz, 1 H), 7.79 -7.86 (m, 2 H), 8.03 (d,  $J = 2.1$  Hz, 1 H), 8.18 (d,  $J = 7.5$  Hz, 1 H), 8.30 (d,  $J = 8.0$  Hz, 1 H), 8.58 (s, 2 H), 11.08 (s, 1 H), 12.05 (s, 1 H). MS (APCI): 320, 322.

20 EXAMPLE 74:

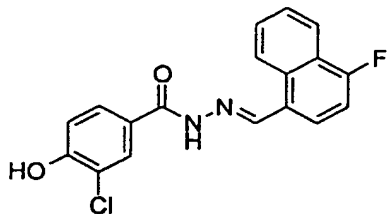
3-Chloro-4-hydroxybenzoic acid (2,4-dichlorobenzylidene)hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.02 (d, J = 8.5 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 7.66 (s, 1 H),  
7.73 (d, J = 8.2 Hz, 1 H), 7.95 (m, 2 H), 8.71 (s, 1 H), 11.97 (s, 1 H), 11.94 (s, 1 H). MS  
5 (APCI): 345.

EXAMPLE 75:

3-Chloro-4-hydroxybenzoic acid (4-fluoro-1-naphthylmethylene)hydrazide

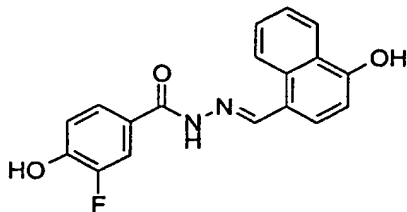


10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.00 (d, J = 8.5 Hz, 1 H), 7.33 (dd, J = 8.2, 10.3 Hz, 1 H), 7.62 - 7.72  
(m, 3 H), 7.82 (m, 1 H), 7.91 (d, J = 1.9 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H), 8.09 (m, 1 H),  
8.91 (s, 1 H), 10.81 (s, 1 H), 11.67 (s, 1 H). MS (APCI): 343.

15 EXAMPLE 76:

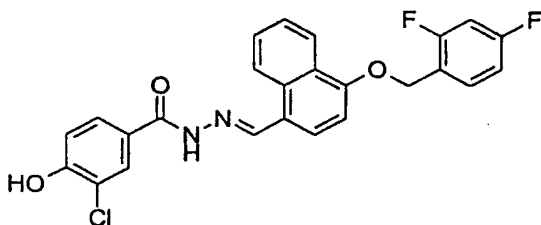
3-Fluoro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.90 (d, J = 8.0 Hz, 1 H), 7.00 (t, J = 8.6 Hz, 1 H), 7.44 - 7.72 (m, 6 H), 8.17 (d, J = 8.6 Hz, 1 H), 8.84 (s, 1 H), 8.89 (d, J = 8.5 Hz, 1 H), 10.60 (s, 1 H), 11.50 (s, 1 H). MS (APCI): 325.

5 EXAMPLE 77:

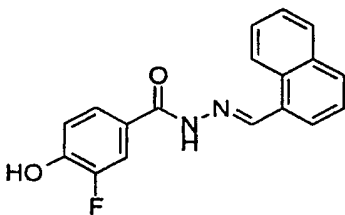
3-Chloro-4-hydroxybenzoic acid [4-(2,4-difluorobenzyloxy)-1-naphthylmethylene]hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.33 (s, 2 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.12 (m, 1 H), 7.21 (d, J = 8.2 Hz, 1 H), 7.31 (m, 1 H), 7.52 (m, 1 H), 7.54 (m, 1H), 7.69 - 7.80 (m, 3 H), 7.94 (s, 1 H), 8.16 (d, J = 8.2 Hz, 1 H), 8.90 (m, 2 H), 10.91 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 467, 469.

EXAMPLE 78:

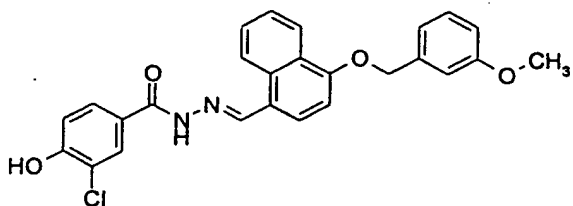
3-Fluoro-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide



MS (APCI): 309.

EXAMPLE 79:

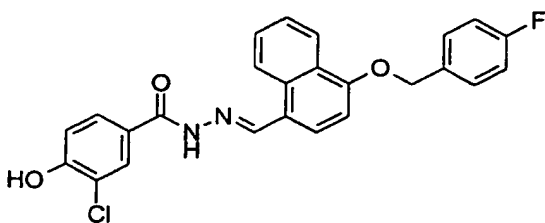
3-Chloro-4-hydroxybenzoic acid [4-(3-methoxybenzyloxy)-1-naphthylmethylene]hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.71 (s, 3 H), 5.29 (s, 2 H), 6.87 (d, J = 8.5 Hz, 1 H), 7.00 - 7.14 (m, 4 H), 7.29 (t, J = 8.0 Hz, 1 H), 7.55 (m, 1 H), 7.68 (m, 1 H), 7.75 (m, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.87 (s, 1 H), 8.92 (d, J = 8.5 Hz, 1 H), 11.00 (s, 1 H),  
 5 11.62 (s, 1 H). MS (APCI): 461.

#### EXAMPLE 80:

3-Chloro-4-hydroxybenzoic acid [4-(4-fluorobenzyloxy)-1-naphthylmethylene]hydrazide

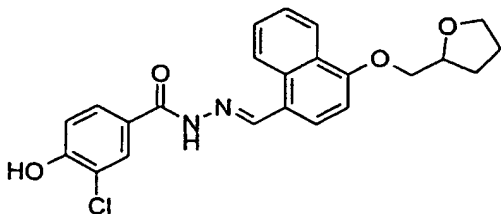


10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.30 (s, 2 H), 7.02 (d, J = 8.5 Hz, 1 H), 7.13 - 7.25 (m, 3 H), 7.53 - 7.60 (m, 4 H), 7.79 (m, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.23 (d, J = 8.0 Hz, 1 H), 8.88 (s, 1 H), 8.92 (d, J = 8.5 Hz, 1 H), 10.93 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 449, 451.

#### 15 EXAMPLE 81:

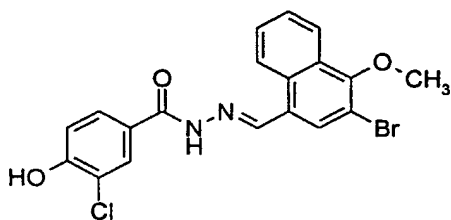
3-Chloro-4-hydroxybenzoic acid [4-(2-tetrahydrofuranylmethoxy)-1-naphthylmethylene]-hydrazide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.77 - 2.04 (m, 4 H), 3.68 (m, 1 H), 3.78 (m, 1 H), 4.12 - 4.16 (m, 2 H), 4.26 (m, 1 H), 7.02 (d,  $J$  = 8.5 Hz, 1 H), 7.04 (d,  $J$  = 8.2 Hz, 1 H), 7.53 (m, 1 H), 7.62 (m, 1 H), 7.74 (m, 2 H), 7.94 (d,  $J$  = 2.0 Hz, 1 H), 8.20 (d,  $J$  = 8.2 Hz, 1 H), 8.87 (s, 1 H), 8.90 (d,  $J$  = 8.5 Hz, 1 H), 10.93 (s, 1 H), 11.61 (s, 1 H). MS (APCI): 425, 427.

5

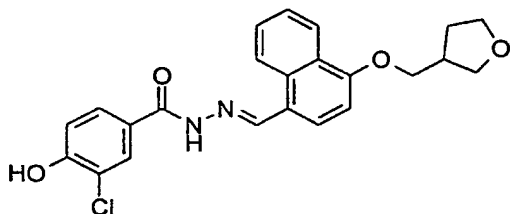
## EXAMPLE 82:

3-Chloro-4-hydroxybenzoic acid (3-bromo-4-methoxy-1-naphthylmethylene)hydrazide

10  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.91 (s, 3 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.65 - 7.76 (m, 3 H), 7.94 (d,  $J$  = 2.0 Hz, 1 H), 8.02 (s, 1 H), 8.12 (d,  $J$  = 8.0 Hz, 1 H), 8.71 (d,  $J$  = 8.0 Hz, 1 H), 8.95 (s, 1 H), 10.96 (s, 1 H), 11.85 (s, 1 H). MS (APCI): 433, 435.

## EXAMPLE 83:

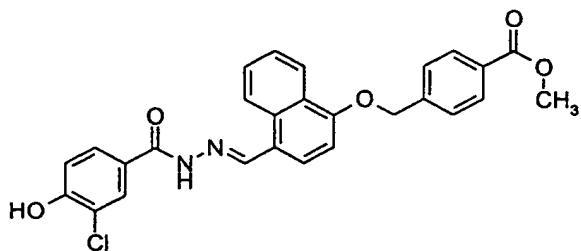
15 3-Chloro-4-hydroxybenzoic acid [4-(3-tetrahydrofuranylmethoxy)-1-naphthylmethylene]-hydrazide



20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.92 (m, 1 H), 2.10 (m, 1 H), 2.77 (m, 1 H), 3.28 - 3.88 (m, 4 H), 4.12 (m, 2 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.04 (d,  $J$  = 8.2 Hz, 1 H), 7.55 (m, 1 H), 7.62 (m, 1 H), 7.74 (d,  $J$  = 8.5 Hz, 1 H), 7.76 (d,  $J$  = 8.0 Hz, 1 H), 7.94 (d,  $J$  = 2.0 Hz, 1 H), 8.20 (d,  $J$  = 8.0 Hz, 1 H), 8.88 (s, 1 H), 8.90 (d,  $J$  = 8.5 Hz, 1 H), 10.91 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 425, 427.

## EXAMPLE 84:

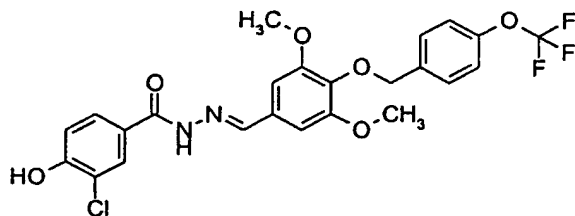
4-(4-[3-Chloro-4-hydroxybenzoyl]hydrazonomethyl]-1-naphthyloxymethyl)benzoic acid methyl ester



- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.80 (s, 3 H), 5.43 (s, 2 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.12 (d,  $J$  = 8.2 Hz, 1 H), 7.54 (m, 1 H), 7.57 (d,  $J$  = 8.0 Hz, 4 H), 7.93 - 7.99 (m, 3 H), 8.30 (d,  $J$  = 8.0 Hz, 1 H), 8.87 (s, 1 H), 8.93 (d,  $J$  = 8.5 Hz, 1 H), 10.91 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 489, 491.

## 10 EXAMPLE 85:

3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-trifluoromethoxybenzyloxy)benzylidene]hydrazide

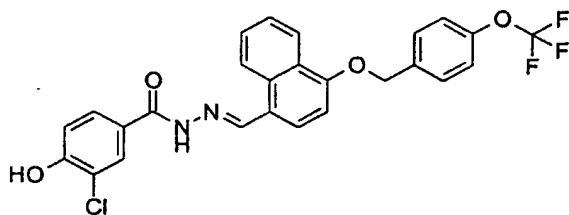


- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.76 (s, 6 H), 4.91 (s, 2 H), 6.95 - 7.00 (m, 3 H), 7.30 (d,  $J$  = 8.2 Hz, 2 H), 7.52 (d,  $J$  = 8.5 Hz, 2 H), 7.68 (d,  $J$  = 2.0, 8.5 Hz, 1 H), 7.88 (s, 1 H), 8.29 (s, 1 H), 10.91 (s, 1 H), 11.69 (s, 1 H). MS (APCI): 525, 527.

## EXAMPLE 86:

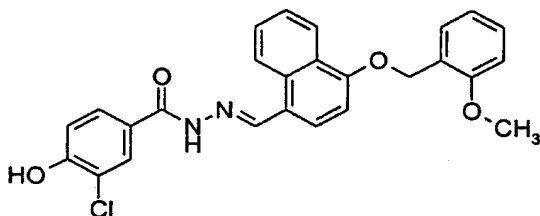
3-Chloro-4-hydroxybenzoic acid [4-(4-trifluoromethoxybenzyloxy)-1-naphthylmethylene]hydrazide

20



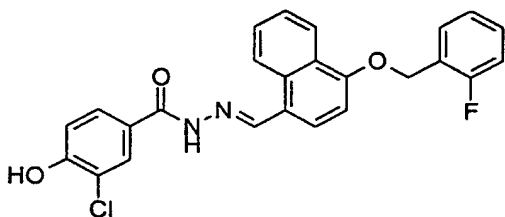
- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.36 (s, 2 H), 7.02 (d, J = 8.4 Hz, 1 H), 7.14 (d, J = 8.2 Hz, 1 H), 7.39 (d, J = 8.2 Hz, 2 H), 7.56 (m, 1 H), 7.62 (m, 3 H), 7.76 (m, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 8.88 (s, 1 H), 8.93 (d, J = 8.5 Hz, 1 H), 10.91 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 515, 517.

## EXAMPLE 87:

3-Chloro-4-hydroxybenzoic acid [4-(2-methoxybenzyloxy)-1-naphthylmethylene]hydrazide

- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.79 (s, 3 H), 5.27 (s, 2 H), 6.95 (m, 1 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.04 (d, J = 8.2 Hz, 1 H), 7.13 (d, J = 8.5 Hz, 1 H), 7.31 (m, 1 H), 7.46 - 7.53 (m, 2 H), 7.61 (m, 1 H), 7.76 (m, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.22 (d, J = 8.3 Hz, 1 H), 8.88 (s, 1 H), 8.92 (d, J = 8.5 Hz, 1 H), 10.90 (s, 1 H), 11.62 (s, 1 H). MS (APCI): 461, 463.

## EXAMPLE 88:

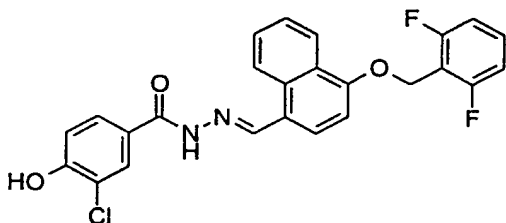
3-Chloro-4-hydroxybenzoic acid [4-(2-fluorobenzyloxy)-1-naphthylmethylene]hydrazide

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  5.36 (s, 2 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.19 - 7.28 (m, 3 H), 7.39 (m, 1 H), 7.53 (m, 1 H), 7.63 (m, 2 H), 7.72 - 7.80 (m, 2 H), 7.94 (d,  $J$  = 2.1 Hz, 1 H), 8.19 (d,  $J$  = 8.3 Hz, 1 H), 8.88 (s, 1 H), 8.92 (d,  $J$  = 8.5 Hz, 1 H), 10.90 (s, 1 H), 11.64 (s, 1 H). MS (APCI): 449, 451.

5

## EXAMPLE 89:

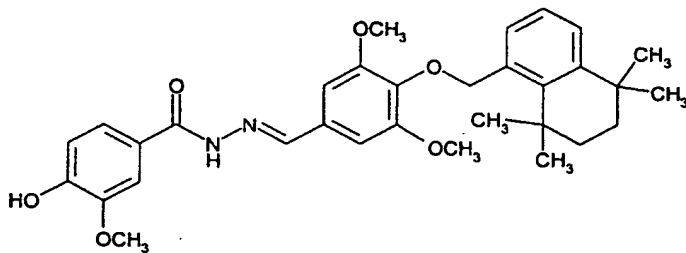
3-Chloro-4-hydroxybenzoic acid [4-(2,6-difluorobenzoyloxy)-1-naphthylmethylene]hydrazide



10  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  5.34 (s, 2 H), 7.03 (d,  $J$  = 8.5 Hz, 1 H), 7.16 (d,  $J$  = 8.2 Hz, 1 H), 7.18 (d,  $J$  = 8.0 Hz, 1 H), 7.27 (d,  $J$  = 8.2 Hz, 1 H), 7.51 (m, 2 H), 7.72 (m, 1 H), 7.74 (d,  $J$  = 8.0 Hz, 1 H), 7.78 (d,  $J$  = 8.0 Hz, 1 H), 7.94 (d,  $J$  = 2.1 Hz, 1 H), 8.03 (d,  $J$  = 8.3 Hz, 1 H), 8.89 (s, 1 H), 8.91 (d,  $J$  = 8.5 Hz, 1 H), 10.97 (s, 1 H), 11.65 (s, 1 H). MS (APCI): 467, 469.

## 15 EXAMPLE 90:

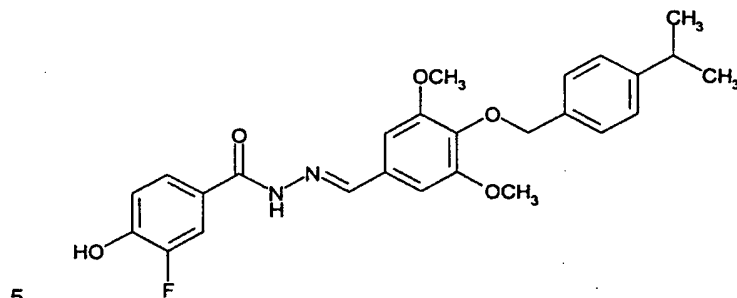
4-Hydroxy-3-methoxybenzoic acid [3,5-dimethoxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-1-ylmethoxy)benzylidene]hydrazide



20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.2 (s, 12H), 1.63 (s, 4H), 3.82 (s, 6H), 3.85 (s, 3H), 4.90 (s, 2H), 6.88 (d, 1H), 7.01 (s, 2H), 7.18 (d, 1H), 7.29 (d, 1H), 7.38 (s, 1H), 7.44 (d, 1H), 7.48 (s, 1H), 8.40 (brd s, 1H), 11.62 (s 1H); MS (APCI): 547.1.

## EXAMPLE 91:

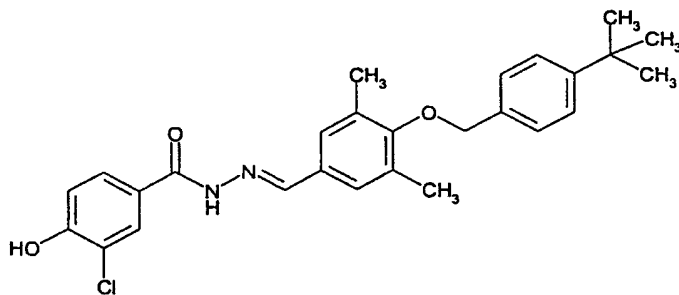
3-Fluoro-4-hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]hydrazide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.05 (d, 6H), 2.67 (m, 1H), 3.61 (s, 6H), 4.69 (s, 2H), 6.79 (s, 2H), 6.86 (t, 1H), 7.01 (d, 2H), 7.24 (d, 1H), 7.44 (dd, 1H), 7.51 (d, 1H), 8.10 (brd s, 1H), 10.32 (s, 1H), 11.41 (s, 1H); MS (APCI): 467.19.

## 10 EXAMPLE 92:

3-Chloro-4-hydroxybenzoic acid [4-(4-tert-butylbenzyloxy)-3,5-dimethylbenzylidene]hydrazide

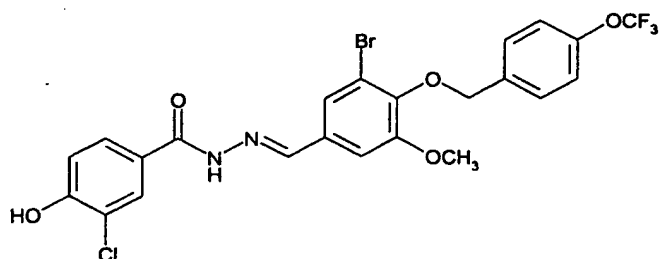


15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.06 (s, 9H), 1.99 (s, 6H), 4.55 (s, 2H), 6.83 (d, 1H), 7.19 (s, 6H), 7.52 (d, 1H), 7.73 (s, 1H), 8.09 (s, 1H), 10.74 (brd s, 1H), 11.44 (s, 1H); MS (FAB): 465.6.

## EXAMPLE 93:

3-Chloro-4-hydroxybenzoic acid [3-bromo-5-methoxy-4-(4-trifluoromethoxybenzyloxy)benzylidene]hydrazide

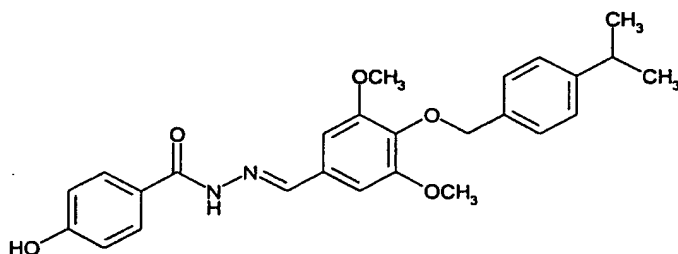
193



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.92 (s, 3H), 5.07 (s, 2H), 7.07 (d, 1H), 7.40 (m, 3H), 7.52 (s, 1H), 7.63 (d, 2H), 7.77 (dd, 1H), 7.97 (d, 1H), 8.35 (s, 1H), 11.00 (brd s, 1H), 11.86 (s, 1H); MS (FAB): 575.0

## EXAMPLE 94:

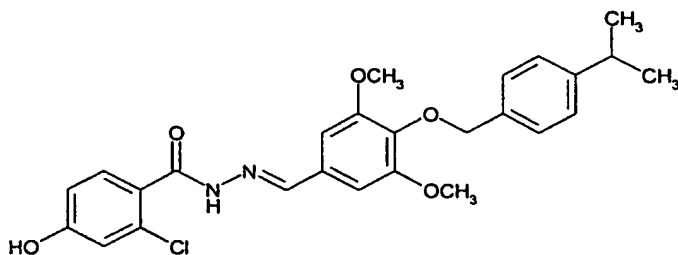
4-Hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]hydrazide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.05 (d, 6H), 2.71 (m, 1H), 3.67 (s, 6H), 4.75 (s, 2H), 6.70 (d, 2H), 6.85 (s, 2H), 7.14 (d, 2H), 7.21 (d, 2H), 7.64 (d, 2H), 8.21 (brd s, 1H), 9.97 (brd s, 1H), 11.47 (s, 1H); MS (APCI): 448.9.

## EXAMPLE 95:

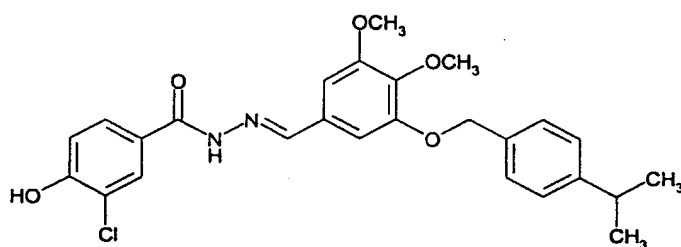
2-Chloro-4-hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]hydrazide:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): d 1.18 (d, 6H), 2.87 (septet, 1H), [3.68 (s, 1H) + 3.81 (s, 5H), 6H], [4.83 (s, 0.5H) + 4.90 (s, 1.5H), 2H], [6.76 (s, 0.5H) + 7.01 (s, 1.5 H), 2H], [6.80 (dd, 1H) + 6.88 (d, 1H), 2H], 7.23 (d, 2H), 7.35 (d, 2H), 7.38 (m, 1H), [7.91 (s, 0.3H) + 8.18 (s, 0.7H), 2H], 10.17 (s, 0.7H) + 11.73 (s, 0.3H), 1H]; MS (APCI): 483.0.

## EXAMPLE 96:

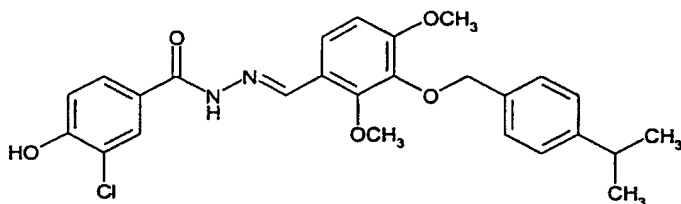
3-Chloro-4-hydroxybenzoic acid [3-(4-isopropylbenzyloxy)-4,5-dimethoxybenzylidene]hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.05 (d, 6H), 2.70 (m, 1H), 3.54 (s, 3H), 3.66 (s, 3H), 4.94 (s, 2H), 6.87 (m, 3H), 7.08 (d, 2H), 7.20 (d, 2H), 7.56 (dd, 1H), 7.77 (s, 1H), 8.15 (s, 1H), 10.76 (s, 1H), 11.52 (s, 1H); MS (APCI): 483.7.

## EXAMPLE 97:

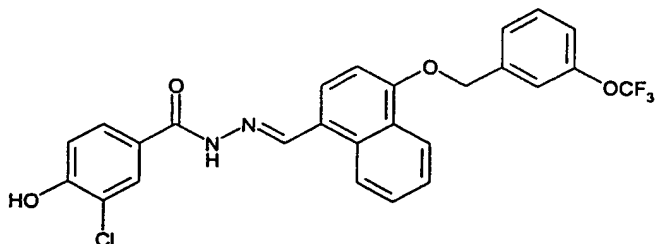
3-Chloro-4-hydroxybenzoic acid [3-(4-isopropylbenzyloxy)-2,4-dimethoxybenzylidene]hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.20 (d, 6H), 2.89 (m, 1H), 3.85 (s, 6H), 4.95 (s, 2H), 6.95 (d, 1H), 7.07 (d, 1H), 7.22 (d, 2H), 7.40 (d, 2H), 7.64 (d, 1H), 7.78 (dd, 1H), 7.97 (d, 1H), 8.62 (s, 1H), 11.68 (s, 1H); MS (APCI): 483.8.

## EXAMPLE 98:

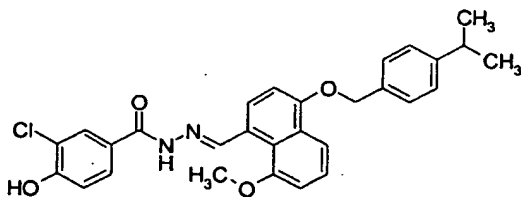
3-Chloro-4-hydroxybenzoic acid [4-(3-trifluoromethoxybenzyloxy)naphth-1-ylmethylene]hydrazide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  5.46 (s, 2H), 7.10 (d, 1H), 7.20 (d, 1H), 7.37 (d, 1H), 7.65 (m, 5H),  
 5 7.82 (m, 2H), 8.01 (s, 1H), 8.32 (d, 1H), 8.97 (m, 2H), 11.70 (s, 1H); MS (APCI): 514.8

EXAMPLE 99:

3-Chloro-4-hydroxy-benzoic acid [4-(4-isopropylbenzyloxy)-8-methoxynaphthalen-1-ylmethylene]hydrazide



4-hydroxy-8-methoxynaphthalene-1-carbaldehyde (2 g, 9.9 mmol) was dissolved in DMF (25 mL). To this mixture potassium carbonate (6.8 g, 50 mmol) and 4-isopropylbenzylchloride  
 15 (1.8 g, 10.4 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. Water (100 mL) was added and the resulting mixture was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to afford 3.0 g crude product. This  
 20 was purified using column chromatography on silica gel (300 mL) eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 2.57 g (81%) of 4-isopropylbenzyloxy-8-methoxynaphthalene-1-carbaldehyde.

Calculated for  $\text{C}_{22}\text{H}_{22}\text{O}_3$ :

C, 79.02%; H, 6.63%. Found:

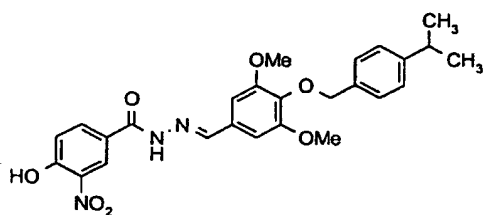
C, 79.10%, H, 6.69%,

C, 79.17%, H, 6.69%.

3-Chloro-4-hydroxybenzoic acid hydrazide (205 mg, 1.1 mmol) was dissolved in DMSO (2 mL) and the above 4-isopropylbenzyloxy-8-methoxynaphthalene-1-carbaldehyde (365 mg, 1.1 mmol) and glacial acetic acid (5 drops) were added and the resulting mixture was stirred at room temperature for 20 minutes. More DMSO (2 mL) was added and the mixture was stirred at room temperature for 16 hours. The solid was collected by filtration and washed successively with DMSO and ethyl acetate to afford 330 mg (66%) of the title compound.

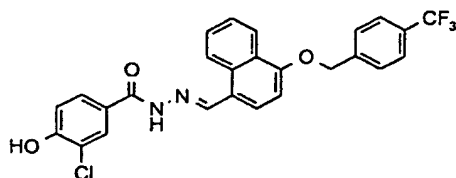
M.p.: > 250 °C.

#### EXAMPLE 100:



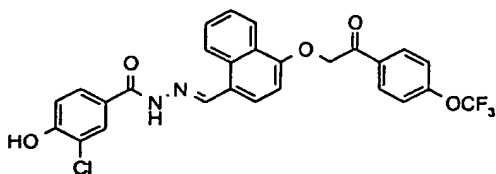
<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) δ 1.13 (d, 6H), 2.82 (sept, 1H), 3.77 (s, 6H), 4.8 (s, 2H), 7.15 (s, 1H), 7.18 (s, 2H), 7.30 (d, 2H), 8.00 (dd, 1H), 8.30 (s, 1H), 8.44 (s, 1H), 11.84 (s, 1H); MS (APCI): 494.0

#### EXAMPLE 101:



<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) δ 5.38 (s, 2H), 6.95 (d, 1H), 7.06 (d, 1H), 7.49 (t, 1H), 7.56 (t, 1H), 7.65-7.71 (m, 6H), 7.87 (d, 1H), 8.22 (d, 1H), 8.80 (s, 1H), 8.86 (d, 1H), 10.82 (s, 1H), 11.55 (s, 1H); MS (FAB): 499

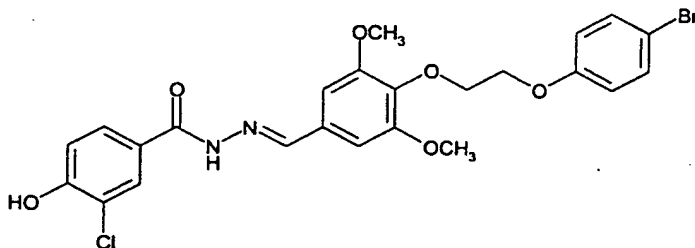
## EXAMPLE 102:



- 5  $^1\text{H}$  NMR ( DMSO- $d_6$  )  $\delta$  5.85 (s, 2H), 7.05 (t, 2H), 7.52-7.63 (m, 4H), 7.73 (m, 2H), 7.95 (s, 1H), 8.16 (d, 2H), 8.33 (d, 1H), 8.90 (s, 1H), 8.93 (s, 1H), 10.90 (brd s, 1H), 11.63 (s, 1H); MS (FAB): 543

## EXAMPLE 103:

- 10 3-Chloro-4-hydroxybenzoic acid {4-[2-(4-bromophenoxy)ethoxy]-3,5-dimethoxybenzylidene}hydrazide

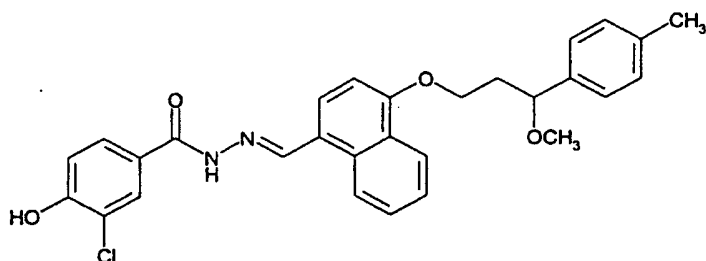


- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.78 (s, 6H), 4.21 (m, 4H), 6.87 (d, 2H), 7.00 (s, 2H), 7.05 (d, 1H), 7.44 (d, 2H), 7.75 (dd, 1H), 7.96 (s, 1H), 8.36 (s, 1H), 10.95 (brd s, 1H), 11.66 (s, 1H); MS(APCI): 548.8.

## EXAMPLE 104:

- 20 3-Chloro-4-hydroxybenzoic acid [4-(3-methoxy-3-(4-methylphenyl)-propyloxy)naphth-1-ylmethylene]hydrazide

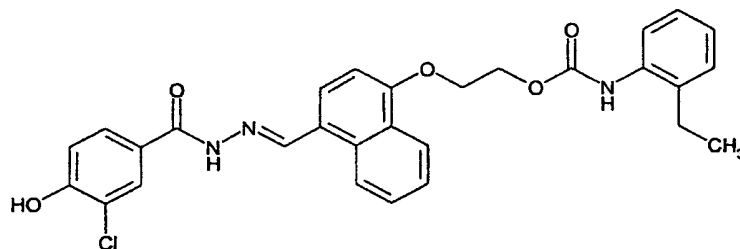
198



MS (APCI): 502.9

## EXAMPLE 105:

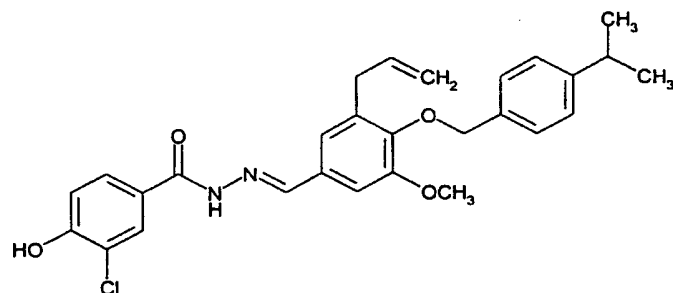
- 5 (2-Ethylphenyl)carbamate acid 2-[4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-naphth-1-yloxy]ethyl ester



- 10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.12 (t, 3H), 2.50 (qt, 2H), 3.69 (t, 2H), 4.39 (t, 2H), 5.20 (t, 1H), 6.57 (t, 1H), 6.74 (d, 1H), 6.97 (d, 1H), 7.08 (m, 3H), 7.57 (t, 1H), 7.67 (t, 1H), 7.81 (t, 2H), 8.01 (s, 1H), 8.35 (d, 1H), 8.95 (m, 2H), 11.67 (s, 1H).

## EXAMPLE 106:

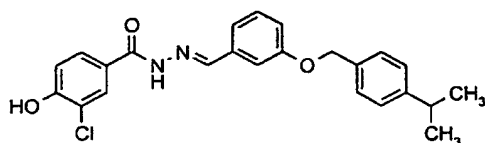
- 15 3-Chloro-4-hydroxybenzoic acid [3-allyl-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene]hydrazide



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ) :  $\delta$  1.13 (d, 6H), 2.80 (m, 1H), 3.20 (m, 2H), 3.85 (s, 3H), 4.82 (s, 2H), 5.00 (d, 2H), 5.70 (m, 1H), 6.96 (s, 1H), 7.05 (s, 1H), 7.20 (d, 2H), 7.30 (d, 2H), 7.70 (d, 1H), 7.89 (s, 1H), 8.28 (s, 1H), 10.80 (brd s, 1H), 11.61 (s, 1H); MS (APCI): 493.1.

Similarly, the following compounds were made:

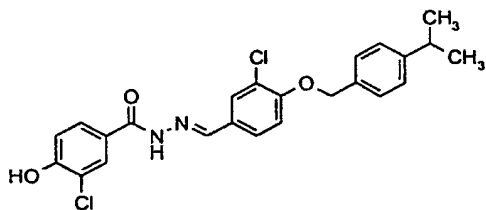
EXAMPLE 107:



5

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  0.99 (d, 6H), 2.68 (septet, 1H), 4.89 (s, 2H), 6.84 (d, 2H), 7.06 (m, 2H), 7.16 (m, 3H), 7.55 (d, 1H), 7.75 (s, 1H), 8.18 (s, 1H), 10.75 (s, 1H), 11.52 (s, 1H); MS (APCI): 423.7, 425.6.

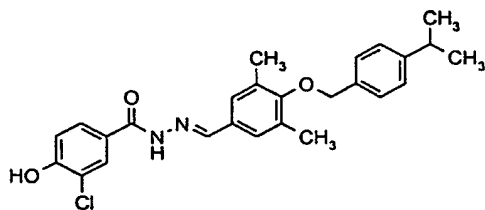
10 EXAMPLE 108:



$^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.18 (d, 1H), 2.88 (septet, 1H), 5.20 (s, 2H), 7.04 (d, 1H), 7.28 (t, 2H), 7.30 (s, 1H), 7.38 (d, 2H), 7.62 (d, 1H), 7.73 (dd, 1H), 7.79 (s, 1H), 7.94 (d, 1H), 8.32 (s, 1H), 11.94 (s, 1H), 11.72 (s, 1H); MS (APCI): 457.4, 459.1.

15

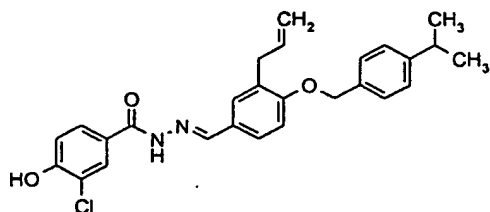
EXAMPLE 109:



$^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.1 (d, 6H), 2.2 (s, 6H), 2.8 (septet, 1H), 4.7 (s, 2H), 7.0 (d, 1H), 7.2 (d, 2H), 7.4 (d, 4H), 7.7 (d, 1H), 7.9 (s, 1H), 8.2 (s, 1H), 10.9 (s, 1H), 11.6 (s, 1H); MS (APCI): 451.6, 453.3.

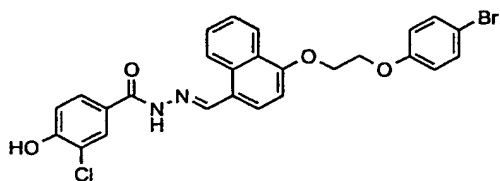
20

## EXAMPLE 110:



- 5 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.1 (d, 6H), 2.8 (septet, 1H), 3.3 (d, 1H), 5.0 (d, 1H), 5.1 (d, 1H), 5.2 (s, 2H), 5.9 (m, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2 (d, 2H), 7.3 (d, 2H), 7.4 (d, 1H), 7.5 (s, 1H), 7.7 (dd, 1H), 7.9 (d, 1H), 8.3 (s, 1H), 10.9 (brd s, 1H), 11.5 (s, 1H); MS (APCI): 463.5, 465.1.

## EXAMPLE 111:

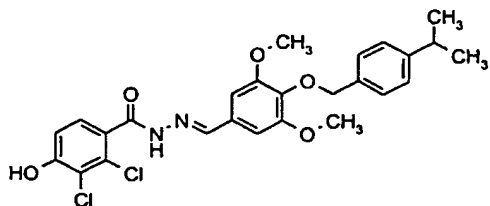


10

- <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 4.47 (t, 2H), 4.54 (t, 2H), 7.01 (d, 2H), 7.07 (d, 1H), 7.14 (d, 1H), 7.45 (d, 2H), 7.53 (t, 1H), 7.27 (d, 1H), 7.79 (m, 2H), 7.96 (d, 1H), 8.17 (d, 1H), 8.91 (s, 1H), 8.94 (d, 1H), 10.92 (s, 1H), 11.64 (s, 1H), MS (APCI): 539.3, 541.1, 543.1.

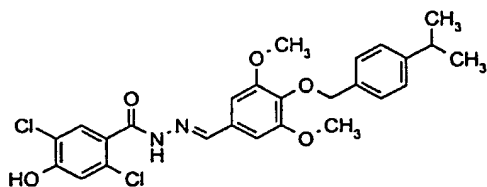
15

## EXAMPLE 112:



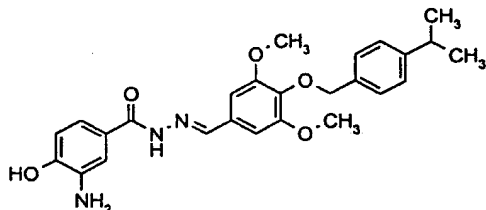
- 20 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.18 (d, 6H), 2.87 (septet, 1H), [3.67 (s, 1.5H) + 3.81 (s, 4.5H), 6H], [4.83 (s, 0.5H) + 4.90 (s, 1.5H), 2H], 6.73 (s, 0.5H) + [7.02 (m, 2.5H), + 7.27 (m, 2.5H) + 7.37 (m, 2.5H), 8H], [7.92 (s, 0.3H) + 8.17 (s, 0.7H), 1H], [10.96 (s, 0.3H) + 11.12 (s, 0.7H), 1H], [11.82 (s, 0.7H) + 11.95 (s, 0.3H), 1H]; MS (APCI): 517.6, 519.2.

## EXAMPLE 113:



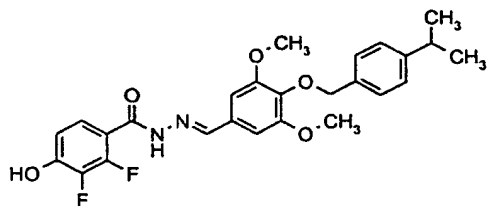
- 5 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.19 (d, 6H), 2.89 (septet, 1H), [3.68 (s, 1.5H) + 3.82 (s, 4.5H), 6H], [4.84 (s, 0.5H) + 4.89 (s, 1.5H), 2H], [6.76 (s, 0.5H) + 7.02 (m, 2.5H), 3H], 7.20 (m, 2H), 7.34 (m, 2H), [7.50 (s, 0.3H) + 7.62 (s, 0.7H), 1H], 7.92 (s, 0.3H) + 8.18 (s, 0.7H), 1H], 11.17 (brd s, 1H), 11.81 (s, 0.7H) + 11.96 (s, 0.3H), 1H]; MS (APCI): 517.7, 519.2.

## 10 EXAMPLE 114:



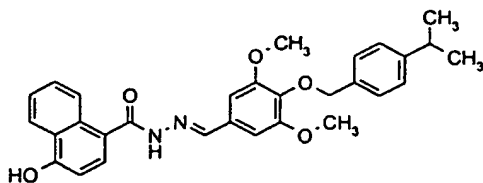
- <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.20 (d, 6H), 2.87 (septet, 1H), 3.82 (s, 6H), 4.89 (s, 2H), 6.69 (d, 1H), 6.98 (m, 3H), 7.21 (m, 3H), 7.36 (d, 2H), 8.32 (s, 1H), 9.8 (brd s, 1H), 11.50 (s, 1H); MS (APCI): 464.7.

## EXAMPLE 115:



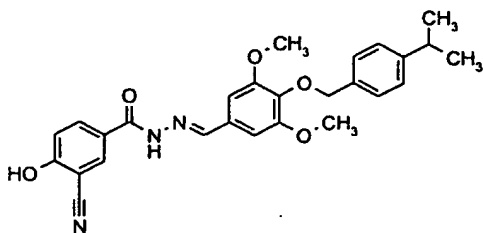
- 20 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.19 (d, 6H), 2.30 (septet, 1H), [3.71 (s) + 3.82 (s), 6H], 4.90 (s, 2H), [6.81 (m, 1.5H) + 6.88 (s, 1.5H), 3H], [7.24 (s, 0.2H) + 8.24 (s, 0.8H), 1H], 11.05 (brd, 1H), 11.69 (s, 0.75H) + 11.94 (s, 0.25H), 1H]; MS (APCI): 485.5, 486.3.

## EXAMPLE 116:



- 5  $^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.19 (d, 6H), 2.88 (septet, 1H), 3.83 (s, 6H), 4.90 (s, 2H), 6.87 (d, 1H), 7.03 (s, 2H), 7.23 (d, 2H), 7.36 (d, 2H), 7.53 (m, 3H), 8.26 (m, 3H), 10.73 (s, 1H), 11.82 (s, 1H); MS (APCI): 499.8.

## EXAMPLE 117:



10

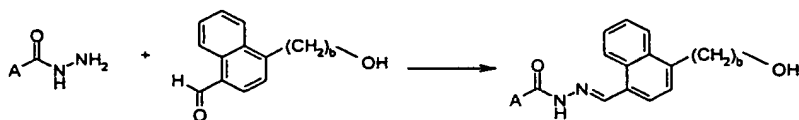
- $^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.20 (d,  $J = 6.9$ , 6H), 2.89 (sept,  $J = 6.9$ , 1H), 3.84 (s, 6H), 4.91 (s, 2H), 7.03 (br s, 2H), 7.12 (d,  $J = 8.8$ , 1H), 7.23 (d,  $J = 8.0$ , 2H), 7.37 (d,  $J = 8.0$ , 2H), 8.04 (dd,  $J = 2.2, 8.8$ , 1H), 8.21 (br s, 1H), 8.35 (br s, 1H), 11.78 (s, 1H), 11.89 (br s, 1H); MS (APCI, neg): 472.

15

Preparation of acyl-hydrazones of 4-(2-hydroxyethyl)-1-naphthaldehyde:

General procedure for synthesis of compounds of the general formula X:

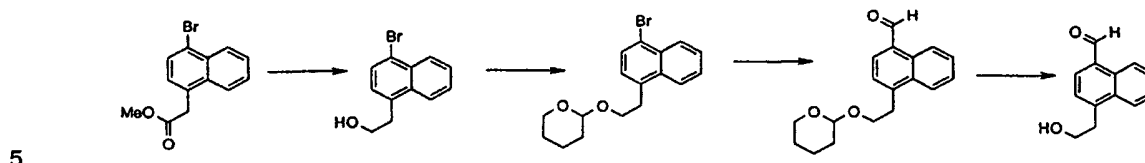
20



formula X

wherein b is 1, 2, 3 or 4

Preparation of 4-(2-hydroxyethyl)-1-naphthaldehyde:



1-Bromo-4-(2-hydroxyethyl)naphthalene:

To a solution of methyl 4-bromo naphthalene acetate (2.0 g, 7.16 mmol) in anhydrous THF (15 mL) was added drop wise at 0°C 1 M lithium aluminum hydride in THF (4 mL). The mixture was stirred at room temperature for 16 h, diluted with water (5 ml), acidified with conc. hydrochloric acid, and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated to provide a 1.71 g (95%) colorless oil (1.71 g, 95%). A similar synthetic reference is described in A. A. Kiprianov, A. A. Shulezhko. Zh. Org. Khim. 2 (1966), 1852, English translation: J. Org. Chem. (USSR) 2 (1966) 1820].

15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 2.36 (s, 1H), 3.33 (t, J = 6.7 Hz, 2H), 3.99 (t, J = 6.7 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.58 - 7.63 (m, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.61 (m, 1H), 8.31 (dd, J = 1.1, 8.0 Hz, 1H). GCMS (pos.) 250, 252.

20 1-Bromo-4-(2-tetrahydropyranyloxyethyl)naphthalene:

To a solution of 1-bromo-4-(2-hydroxyethyl)naphthalene (1.71 g, 6.8 mmol) in dichloromethane (20 mL) was added 3,4-dihydro-2H-pyran (1 mL, 0.92 g, 11.0 mmol) and p-toluene sulfonic acid (80 mg). The mixture was stirred at room temperature for 90 min, diluted with dichloromethane (20 mL), washed with satd. NaHCO<sub>3</sub> sol. (20 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography using hexane/ethyl acetate 9:1 as eluent provided 1.69 g (75%) of a colorless oil.

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 1.51 -1.60 m (6H), 3.37 (t, J = 7.2 Hz, 2H), 3.39 - 3.47 (m, 1H), 3.74 (t, J = 7.2 Hz, 2H), 4.08 (dd, J = 2.4, 7.5 Hz, 1H), 4.60 (m, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.56 -

7.61 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 8.09 - 8.12 (m, 1H), 8.29 (dd, J = 2.5, 7.1 Hz, 1H). GCMS (pos), 334, 336.

1-Formyl-4-(2-tetrahydropyranyloxyethyl)naphthalene:

- 5 A solution of 1-bromo-4-(2-tetrahydropyranyloxyethyl)naphthalene in anhydrous THF (15 mL) under nitrogen was cooled to -78°C. n-Butyl lithium (1.4 mL of a 2.5 M solution in hexane) was added via syringe, and the mixture was stirred at the same temperature for 30 min. DMF (1.1 mL) was added, and the mixture was allowed to reach room temperature. It was diluted with satd. NH<sub>4</sub>Cl solution (10 mL), extracted with ether (3 x 10 ml), dried (MgSO<sub>4</sub>) and  
10 concentrated. Flash chromatography using hexane/ethyl acetate 5:1 as eluent provided 408 mg (54%) of a colorless oil.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 1.48 - 1.69 m (6H), 3.45 - 3.50 (m, 3H), 3.69 - 3.85 (m, 2H), 4.07 - 4.17 (m, 1H), 4.61 (m, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.62 - 7.73 (m, 2H), 7.92 (d, J = 7.3 Hz, 1H),  
15 8.20 (d, J = 1.0, 8.1 Hz, 1H), 10.36 (s, 1H). GCMS: 284

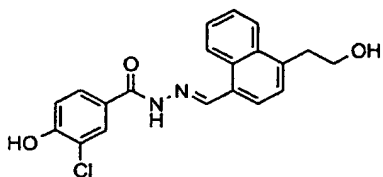
1-Formyl-4-(2-hydroxyethyl)naphthalene:

- 1-Formyl-4-(2-tetrahydropyranyloxyethyl)naphthalene (400 mg, 1.40 mmol) was dissolved in methanol (15 mL), and p-toluene sulfonic acid (45 mg) was added. The mixture was stirred  
20 at room temperature for 16 h, and concentrated. The residue was dissolved in ethyl acetate (3 x 10 mL), washed with satd. NaHCO<sub>3</sub> (20 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by flash chromatography using hexane/ethyl acetate 3:1 as eluent provided 182 mg (65%) of a colorless oil .

- 25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 2.09 (s, 1H), 3.40 (t, J = 6.6 Hz, 2H), 4.02 (t, J = 6.6 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.61 - 7.71 (m, 2H), 7.88 (d, J = 7.3 Hz, 1H), 8.13 (dd, J = 1.3, 8.0 Hz, 1H), 9.29 (dd, J = 1.3, 8.0 Hz, 1H), 10.28 (s, 1H). GCMS: 200

- The following compounds were prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 1-formyl-4-(2-hydroxyethyl) naphthalene (from step D) with 4-hydroxy benzoic acid hydrazides.  
30

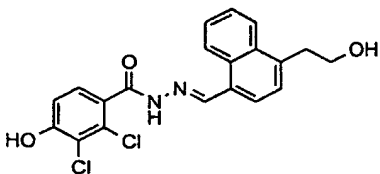
## EXAMPLE 118:



- 5 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ = 3.25 (t, J = 6.5 Hz, 2H), 3.73 (dt, J = J' = 6.5 Hz, 2H), 4.84 (t, J = 6.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 7.4 Hz, 1H), 7.60 - 7.68 (m, 2H), 7.80 (dd, J = 1.8, 7.4 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 9.19 (d, J = 6.7 Hz, 1H), 8.85 (d, J = 7.7 Hz, 1H), 9.05 (s, 1H), 10.98 (s, 1H), 11.76 (s, 1H); MS (APCI, pos.): 369.4, 371.2.

10

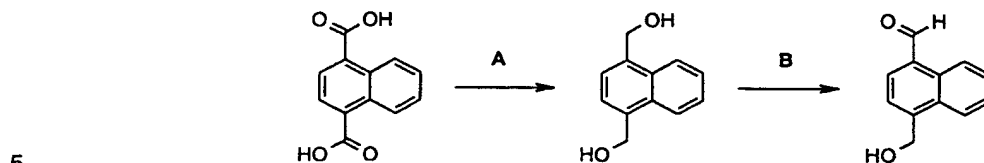
## EXAMPLE 119:



- 15 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ = 3.18 (t, J = 7.0 Hz, 1H), 3.25 (t, J = 7.0 Hz, 1H), 3.65 (dd, J = 7.0 Hz, 1H), 3.74 (dd, J = 5.3, 7.0 Hz, 1H), 4.74 (t, J = 5.3 Hz, 0.5H), 4.79 (t, J = 5.3 Hz, 0.5H), 7.04 (d, J = 8.3 Hz, 0.5H), 7.05 (d, J = 8.3 Hz, 0.5H), 7.25 (d, J = 8.3 Hz, 0.5H), 7.28 (d, J = 8.3 Hz, 0.5H), 7.38 (d, J = 7.4 Hz, 0.5H), 7.43 (d, J = 8.4 Hz, 0.5H), 7.47 - 7.57 (m, 1.5H), 7.61-7.72 (m, 1H), 7.82 (d, J = 7.2 Hz, 0.5H), 8.10 (d, J = 8.6 Hz, 0.5H), 8.19 (dd, J = 2.2, 7.2 Hz, 0.5H), 8.45 (d, J = 8.6 Hz, 0.5H), 8.48 (s, 0.5H), 8.85 (s, 0.5H), 8.87 (dd, J = 2.2, 6.5 Hz, 0.5H), 11.00 (s, 0.5H), 11.15 (s, 0.5H), 11.86 (s, 0.5H), 11.92 (s, 0.5H); MS (APCI, pos.): 403.4, 405.2, 406.1.
- 20

25

Preparation of acylhydrazones of 4-hydroxymethylnaphthaldehyde:



Step A:

The 1,4-Naphthalenedicarboxylic acid (25 g, 116 mmol) was dripped into a mixture of Lithium Aluminum Hydride (15 g, 395 mmol) in 600 mL of anhydrous THF and refluxed for two  
10 days. The mixture was cooled in an ice bath and excess LAH was decomposed by the slow addition of methanol followed by ice chips. THF was removed under vacuum and the residue was acidified with 1N HCl. The product was extracted with ethyl acetate (3x), washed with aqueous sodium bicarbonate (3x), water, brine, and dried over magnesium sulfate. 1,4-Bishydroxymethylnaphthalene (70%) was obtained as a solid after evaporation of the solvent  
15 and can be used in the subsequent oxidation step without further purification. A portion of the material was purified by column chromatography using hexane/ethyl acetate (80/20 to 75/25) for characterization purposes.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 5.19 (s, 4H), 7.77 (m, 4H), 8.32 (m, 2H).

20

Step B:

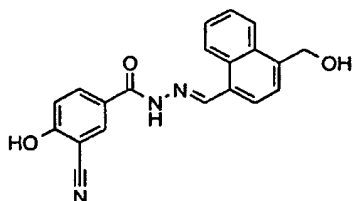
To a solution of 1,4-bishydroxymethylnaphthalene (12 g, 65 mmol) in ethyl acetate (300 ml) was added manganese dioxide (28 g, 325 mmol). After stirring for 45 minutes most of the starting material had disappeared and two new spots (mono aldehyde and dialdehyde) were  
25 seen on TLC. The upper spot corresponds to the dialdehyde. The mixture was passed through a bed of Celite and eluted with additional volumes of ethyl acetate. The solvent was evaporated and 4-hydroxymethylnaphthaldehyde was purified by column chromatography using hexane/ethyl acetate (80/20 to 75/25) in 50% yield.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 5.19 (s, 2H), 5.71 (brd s, 1H), 7.73 (t, 1H), 7.78 (t, 1H), 7.95 (d, 1H),  
30 8.26 (m, 2H), 9.34 (d, 1H), 10.46 (s, 1H).

Examples of products employing the above aldehyde:

5

EXAMPLE 120:

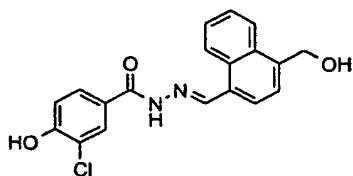


10 The above compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the above aldehyde with 3-cyano-4-hydroxybenzoic acid hydrazide.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 5.02 (s, 2H), 5.44 (s, 1H), 7.14 (d, 1H), 7.69 (m, 3H), 7.91 (d, 1H), 8.10 (d, 1H), 8.14 (d, 1H), 8.27 (s, 1H), 8.87 (d, 1H), 9.06 (s, 1H), 11.84 (brd s, 2H); MS (ACPI): 346.3, 347.2.

15

EXAMPLE 121:

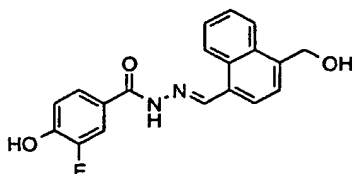


20 The above compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the above aldehyde with 3-chloro-4-hydroxybenzoic acid hydrazide.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 5.02 (s, 2H), 5.43 (t, 1H), 7.10 (d, 1H), 7.66 (m, 3H), 7.80 (d, 1H), 7.90 (d, 1H), 8.02 (s, 1H), 8.15 (d, 1H), 8.87 (d, 1H), 9.08 (s, 1H), 10.98 (s, 1H), 11.79 (s, 1H); MS (APCI): 355.5

25

## EXAMPLE 122:



5

The above compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the above aldehyde with 3-fluoro-4-hydroxybenzoic acid hydrazide.

10 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 4.84 (s, 2H), 6.91 (t, 1H), 7.43-7.53 (m, 4H), 7.62 (d, 1H), 7.72 (d, 1H), 7.96 (d, 1H), 8.68 (d, 1H), 8.98 (s, 1H), 11.71 (brd s, 1H); MS (APCI): 339.4, 340.3.

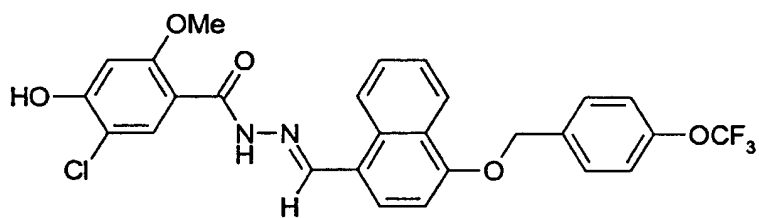
The compounds of formula II can also be prepared by parallel synthesis using the protocol mentioned above in a combinatorial approach. Thousands of compounds of formula II can thus  
15 be prepared by this combinatorial approach which can be semi- or fully automated. The automation of this protocol can be performed using solution phase combinatorial chemistry in e.g. a 96 well setup using an automated synthesizer device. In the first step of the synthesis the aldehydes or ketones may be prepared according to Scheme II by a combination of a selected number of aldehydes or ketones with a selected number of alkylating reagents. In the second  
20 step the formed aldehydes/ketones can be combined with a selected number of the hydrazides (which may be synthesized according to Scheme I) thereby generating a predetermined very large number of compounds as single entities.

The synthesized compounds mentioned above are examples of such compounds that can be  
25 prepared using this combinatorial methodology.

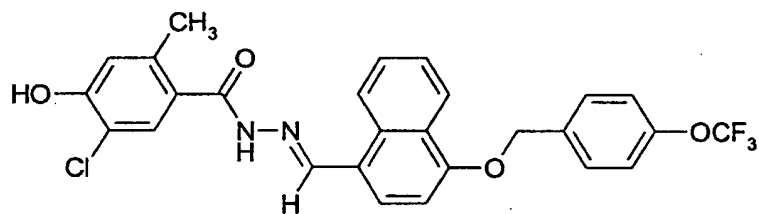
By application of the above methodology, the following compounds may also be synthesized:

## EXAMPLE 123:

5

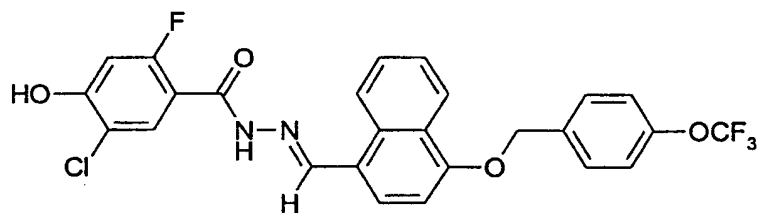


## EXAMPLE 124:



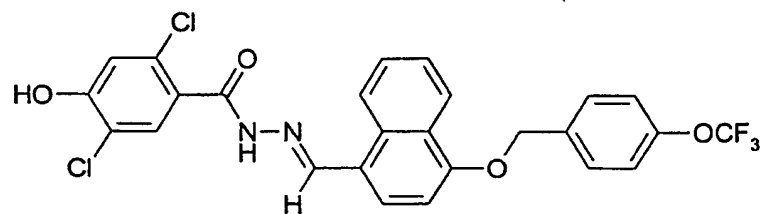
10

## EXAMPLE 125:

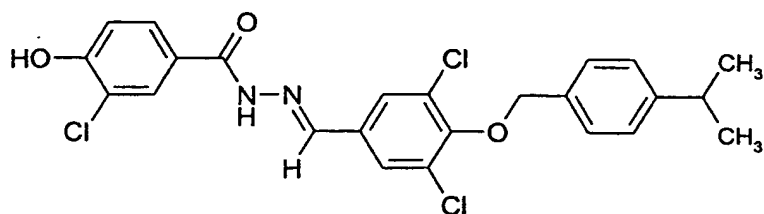


15

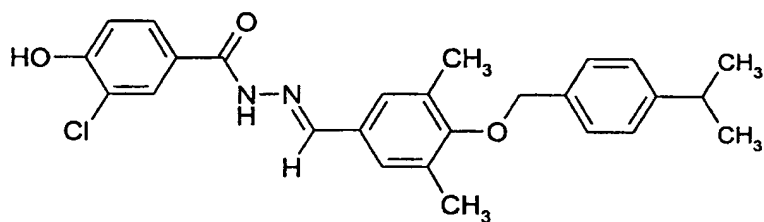
## EXAMPLE 126:



## EXAMPLE 127:

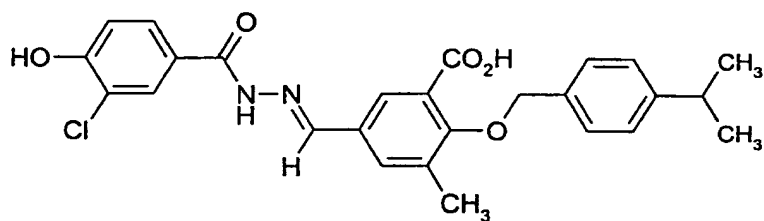


## EXAMPLE 128:

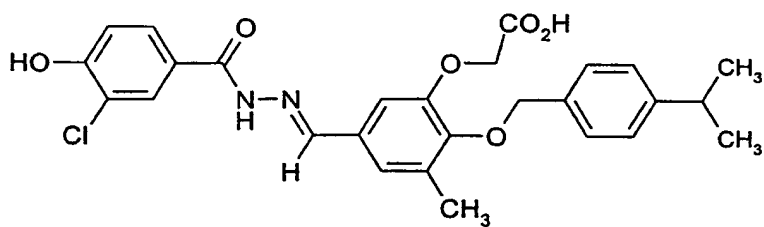


5

## EXAMPLE 129:

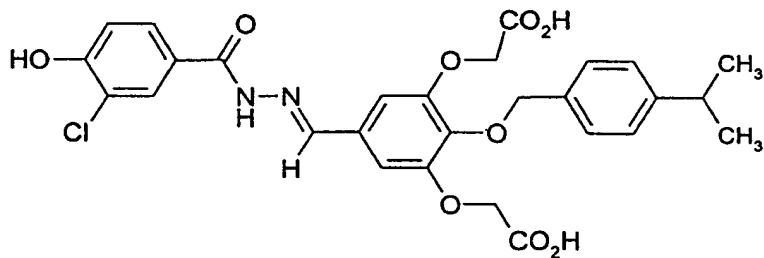


## EXAMPLE 130:

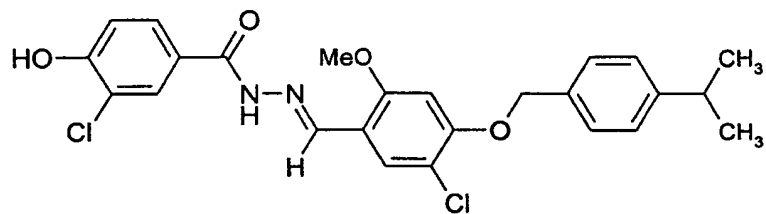


10

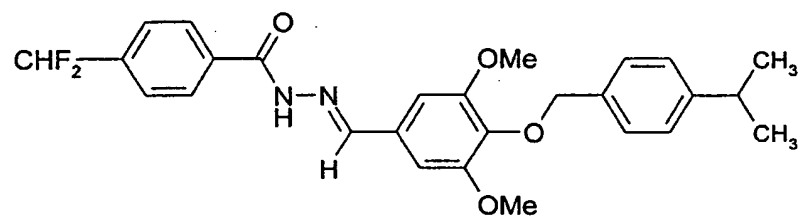
## EXAMPLE 131:



## EXAMPLE 132:

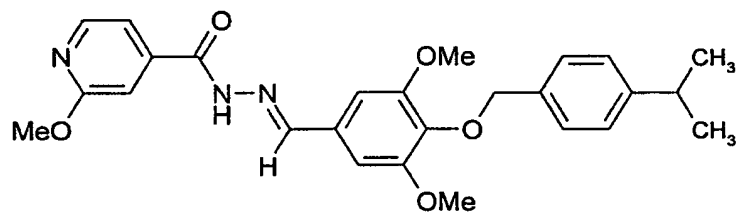


## EXAMPLE 133:

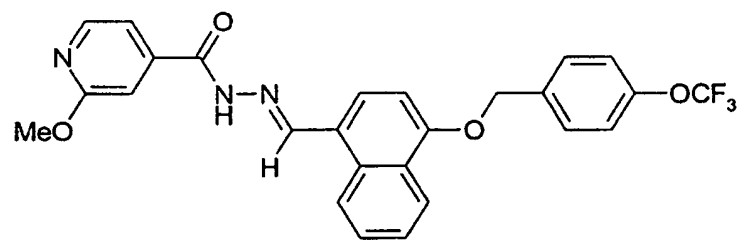


5

## EXAMPLE 134:

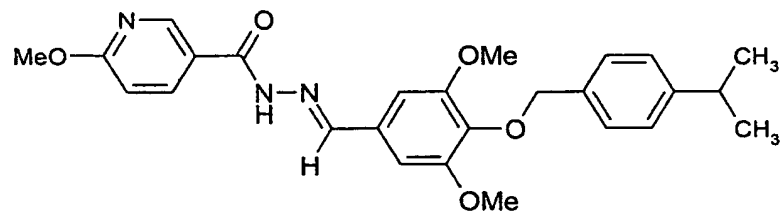


## EXAMPLE 135:

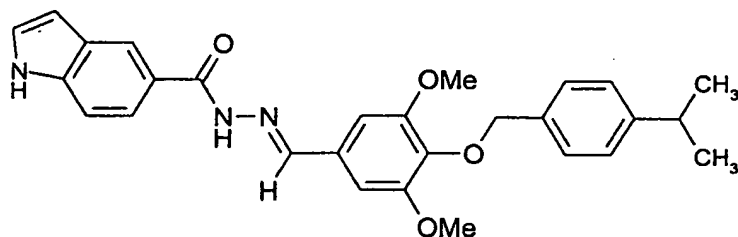


10

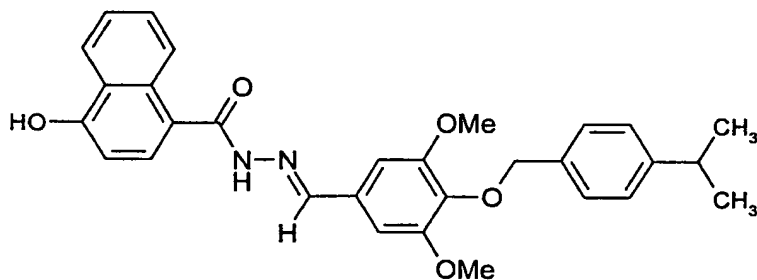
## EXAMPLE 136:



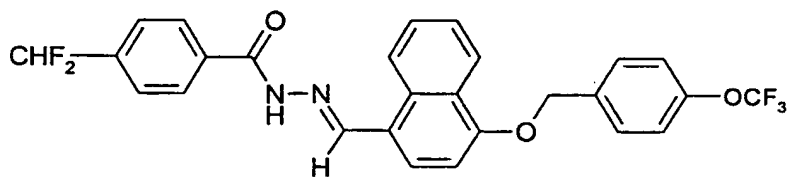
## EXAMPLE 137:



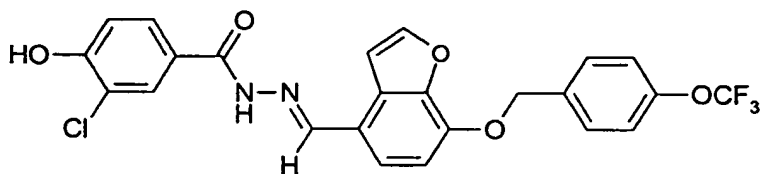
## 5 EXAMPLE 138:



## EXAMPLE 139:

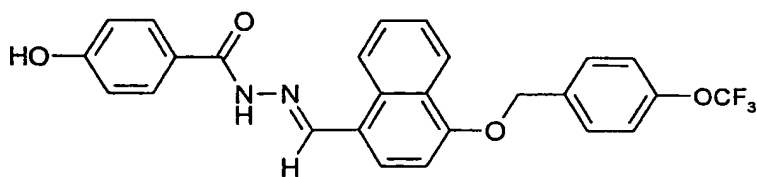


## EXAMPLE 140:

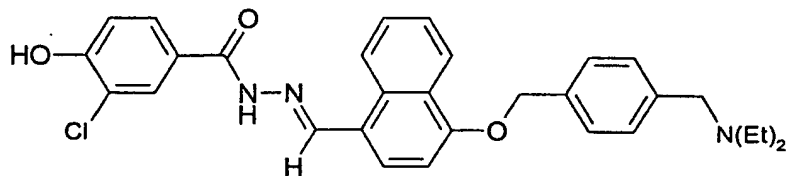


10

## EXAMPLE 141:

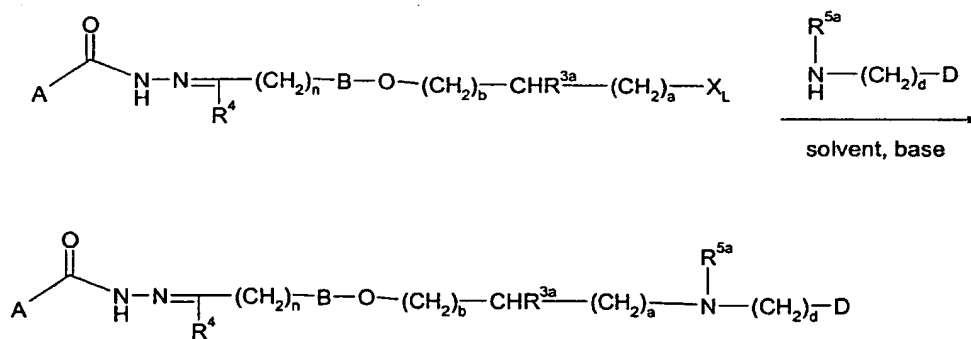


## EXAMPLE 142:

General procedure for the synthesis of further derivatized hydrazides of formula II:

- 5 The compounds of general formula I may be prepared according to one embodiment of the invention, the alkyldene hydrazides of general formula II, as indicated in Scheme III, that is, by converting an alkyldene hydrazide (prepared according to the general method shown in Scheme I, and more specifically as in example 8) into a further derivatized alkyldene hydrazide. Thus, by reacting an amine with an alkyldene hydrazide that contains a leaving group  $X_L$
- 10 (Scheme III) a new alkyldene hydrazide containing an amine in the group K of formula II can be formed.

SCHEME III

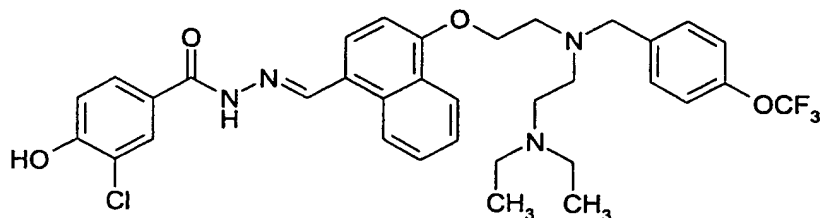


15

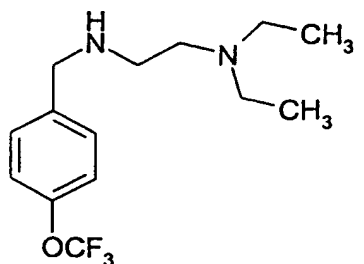
wherein A, B, D, n,  $R^4$ ,  $R^{3a}$ , b and d are as defined for formula I and  $R^{5a}$  is lower alkyl. Specific examples illustrating the preparation of further derivatized hydrazides of formula II are provided below:

20 EXAMPLE 143:

3-Chloro-4-hydroxybenzoic acid {4-[2-[N'-(2-N,N-diethylaminoethyl)-N'-(4-trifluoromethoxybenzylamino)]]ethoxy-1-naphthylmethylene}hydrazide



5 N,N-diethyl-N'-(4-trifluoromethoxybenzyl)ethylenediamine:



A solution of (4-trifluoromethoxy)benzaldehyde (1.9 g, 10 mmoles), N,N-diethylethylenediamine (1.16 g, 10 mmoles), zinc chloride (1.36 g, 10 mmoles) and sodium cyanoborohydride (1.26 g, 20 mmoles) in methanol (10 mL) in a dry 100 mL round-bottom flask was stirred at room temperature for 8 hours. Water (20 mL) was then added and most of the methanol was removed in vacuo. The residue was distributed between ethyl acetate and 1N HCl. The acidic aqueous phase was basified with excess of sodium hydroxide. Crude N,N-diethyl-N'-(4-trifluoromethoxybenzyl)ethylenediamine was obtained. The crude product was used in the following reaction without further purification.

15

MS (CI): 291. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.4 (m, 2H), 7.2 (m, 2H), 3.9 (bs, 2H), 3.1-2.6 (m, 9H), 1.4-1.1 (t, 6H).

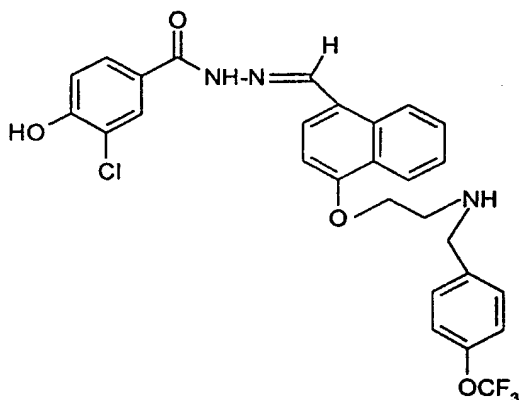
To a flask containing N,N-diethyl-N'-(4-trifluoromethoxybenzyl)ethylenediamine (0.29 g, 1 mmole) in DMF (5 mL) was added [1-(4-chloroethoxy)naphthyl](3-chloro-4-hydroxy)benzoic acid hydrazide (0.41g, 1 mmole) and triethylamine (0.1 g, 1mmole). The resulting solution was heated at 80°C overnight. Removal of most of the solvent in vacuo followed by flash chromatography (10:1 CHCl<sub>3</sub>/MeOH) on silica gel provided the title compound as a brown solid.

<sup>1</sup>HNMR (DMSO-d<sub>6</sub>): δ 11.7 (1H), 9.0 bs, 2H), 8.4-7.0 (m, 12 H), 4.75 (bs, 1H), 4.65 (bs, 1H), 4.55 (t, 1H), 4.35 (t, 1H), 4.15 (t, 1H), 3.9 (bs, 1H), 3.5 (q, 4H), 3.05 (t, 1H), 1.3 (t, 3H), 0.95 (t, 3H). M.p.: 134-136°C. MS (CI): 657, 659.

5

## EXAMPLE 144:

3-Chloro-4-hydroxybenzoic acid [4-[2-(4-trifluoromethoxy)benzylaminoethoxy]-1-naphthylmethylene]hydrazide



10 To a flask containing 4-trifluoromethoxybenzylamine (0.29 g, 1 mmole) in DMF (5 mL) was added 3-chloro-4-hydroxybenzoic acid [4-(2-chloroethoxy)-1-naphthylmethylene]hydrazide (0.403g, 1 mmole) and triethylamine (0.1 g, 1mmole). The resulting solution was heated at 80°C for 16 hours. Removal of most of the solvent in vacuo, followed by flash chromatography (10:1 CHCl<sub>3</sub>/MeOH) on silica gel provided the title compound as a brown solid.

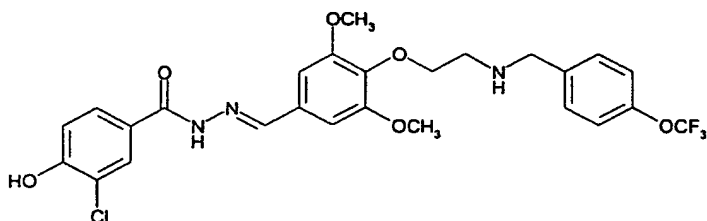
15

<sup>1</sup>HNMR (DMSO-d<sub>6</sub>): δ 11.6 (s, 1H), 9.0 (m 2H), 8.3 (m 1H), 8.0 (m,1H), 7.8 (s, 2H), 7.7 (m,1H), 7.6 (m, 1H), 7.5 (m, 3H), 7.3 (m, 2H), 7.1 (m, 2H), 4.3 (t, 2H), 3.9 (s, 2H), 3.0 (t, 2H). MS (CI): 557, 559.

20 By application of the above methodology the following compounds of the invention were synthesized:

## EXAMPLE 145:

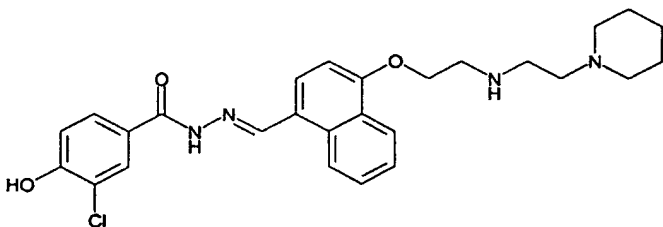
3-Chloro-4-hydroxybenzoic acid {3,5-dimethoxy-4-[2-(4-trifluoromethoxybenzylamino)ethoxy]benzylidene}hydrazide



<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.90 (brd t, 2H), 3.75 (s, 6H), 3.89 (s, 2H), 4.08 (brd t, 2H), 6.87 (d, 1H), 7.10 (s, 2H), 7.20 (d, 2H), 7.43 (d, 2H), 7.65 (m, 1H), 7.82 (m, 1H), 8.11 (brd s, 1H); MS (APCI): 567.9.

EXAMPLE 146:

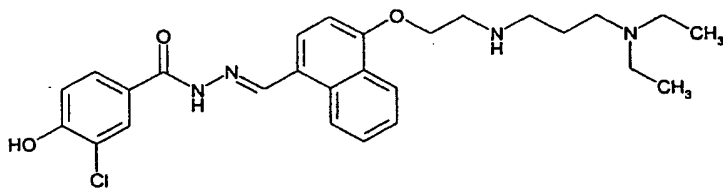
10 3-Chloro-4-hydroxybenzoic acid {4-[2-(2-piperidin-1-yl-ethylamino)ethoxy]naphth-1-ylmethylene}hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.53 (m, 2H), 1.74 (m, 4H), 3.12 (m, 2H), 3.40 (m, 2H), 3.54 (m, 2H), 3.63 (m, 4H), 4.52 (s, 2H), 7.10 (d, 1H), 7.14 (d, 1H), 7.60 (t, 1H), 7.71 (m, 1H), 7.80 (dd, 1H), 7.83 (d, 1H), 8.00 (d, 1H), 8.51 (d, 1H), 8.95 (d, 1H), 8.98 (s, 1H), 11.69 (s, 1H); MS (APCI): 495.0

EXAMPLE 147:

20 3-Chloro-4-hydroxybenzoic acid {4-[2-(3-diethylaminopropylamino)ethoxy]naphth-1-ylmethylene}hydrazide

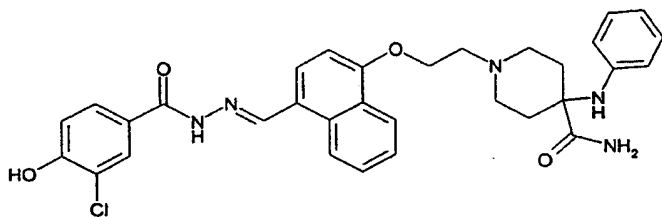


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.21 (t, 6H), 2.10 (m, 2H), 3.14 (m, 10H), 4.52 (t, 2H), 7.10 (d, 1H), 7.14 (d, 1H), 7.63 (t, 1H), 7.73 (m, 1H), 7.80 (dd, 1H), 7.84 (d, 1H), 8.00 (d, 1H), 8.46 (d, 1H), 8.93 (s, 1H), 8.98 (m, 1H), 9.20 (m, 2H), 9.69 (m, 1H), 11.00 (s, 1H), 11.69 (s, 1H);

5 MS (APCI): 497.0.

#### EXAMPLE 148:

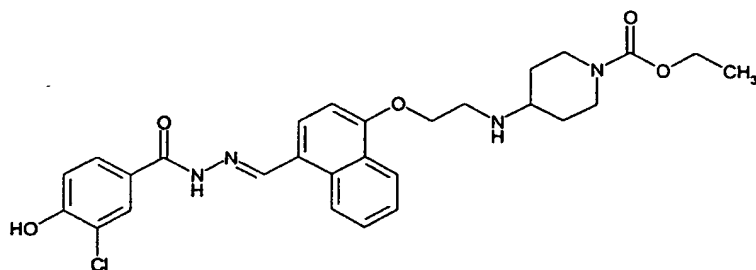
10 1-(2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}ethyl)-4-phenylaminopiperidine-4-carboxylic acid amide



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.16 (m, 2 H), 1.88 (m, 2H), 2.03 (m, 2H), 2.80 (m, 2H), 2.92 (m, 2H), 4.37 (m, 2 H), 4.40 (brd s, 2H), 4.44 (s, 1 H), 6.55 - 6.62 (m, 3 H), 6.96 (s, 1 H), 7.03-  
15 7.16 (m, 5H), 7.61(dd, 1H), 7.68 (dd, 1 H), 8.00 (d, 1H), 8.27 (d, 1H), 8.94 (s, 1 H), 8.97 (s, 1H), 11.63 (s, 1H); MS (APCI): 586.4

#### EXAMPLE 149:

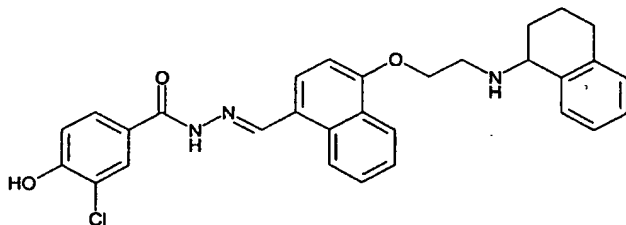
20 4-(2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}ethylamino)piperidine-1-carboxylic acid ethyl ester



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.10 (t, 3H), 1.15 - 1.23 (m, 2H), 1.86 (m, 2H), 2.79 (m, 3H), 3.30 (m, 2H), 3.87 (m, 2H), 3.94 (q, 2H), 4.28 (m, 2H), 7.03 (d, 1H), 7.05 (m, 1H), 7.51 - 7.63 (m, 3H), 7.13 (d, 1H), 7.75 (m, 1H), 7.93 (d, 1H), 8.29 (d, 1H), 8.87 (m, 2H), 11.55 (s, 1H); MS (APCI): 539.1, 541.0.

#### EXAMPLE 150:

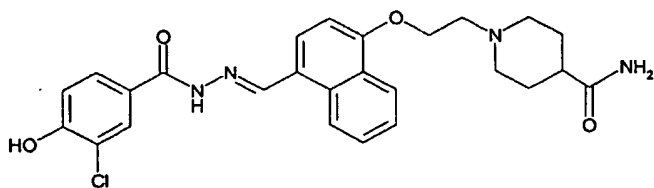
3-Chloro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydronaphth-1-ylamino)ethoxy]-naphth-1-ylmethylene}hydrazide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.76 (m, 1H), 2.04 (m, 1H), 2.17 (m, 2H), 2.75 - 2.94 (m, 2H), 3.61 (m, 2H), 4.55 (m, 2H), 4.71 (s, 1H), 7.11 (d, 1H), 7.13 (d, 1H), 7.23 - 7.35 (m, 3H), 7.61 (d, 1H), 7.67 (d, 1H), 7.71 (dd, 1H), 7.81 (dd, 1H), 7.86 (d, 1H), 8.01 (d, 1H), 8.48 (d, 1H), 8.94 (m, 1H), 8.99 (m, 1H), 9.22 (m, 2H), 11.00 (s, 1H), 11.64 (s, 1H); MS (APCI): 514.0, 516.0

#### EXAMPLE 151:

1-(2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}ethyl)piperidine-4-carboxylic acid amide

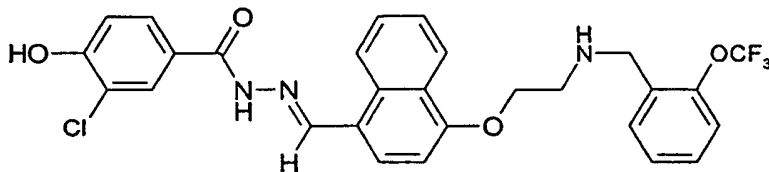


MS (APCI): 495.0

EXAMPLE 152:

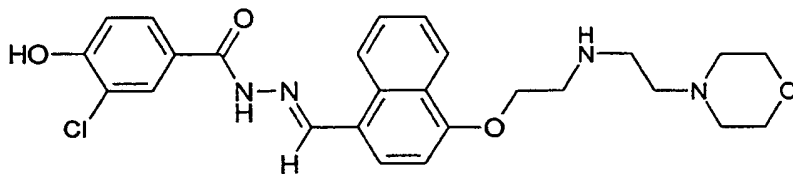
5

3-Chloro-4-hydroxybenzoic acid {4-[2-(2-trifluoromethoxybenzylamino)-ethoxy]-1-naphthyl-methylene}hydrazide



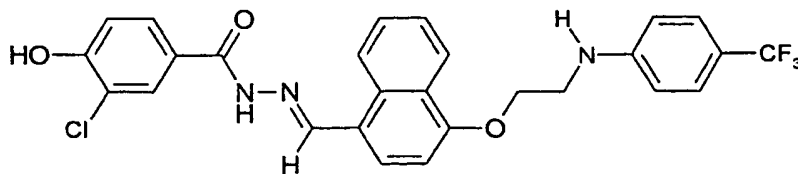
10 EXAMPLE 153:

3-Chloro-4-hydroxybenzoic acid {4-[2-(4-morpholinylethylamino)ethoxy]-1-naphthylmethylene}-hydrazide

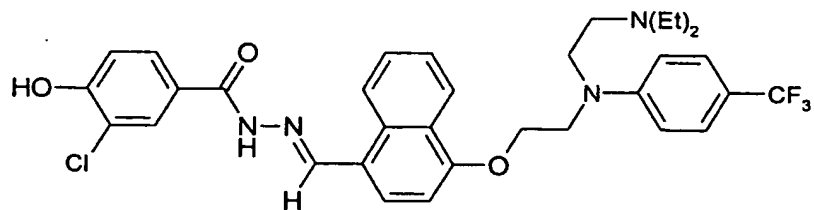


15 By application of the above methodology the following compounds may also be synthesized:

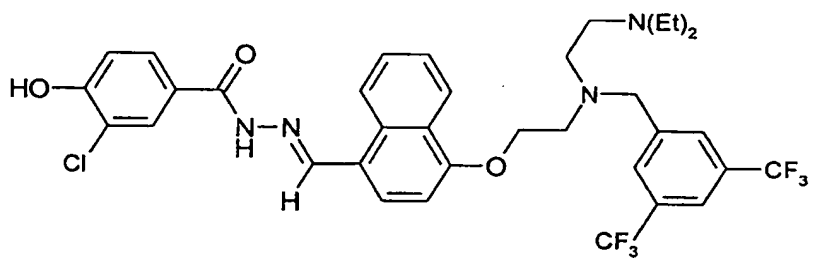
EXAMPLE 154:



## EXAMPLE 155:

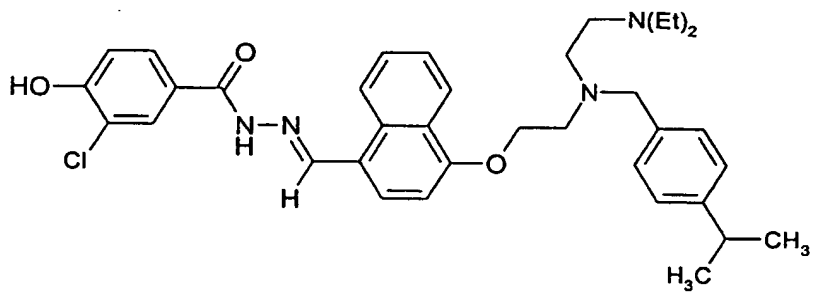


## EXAMPLE 156:

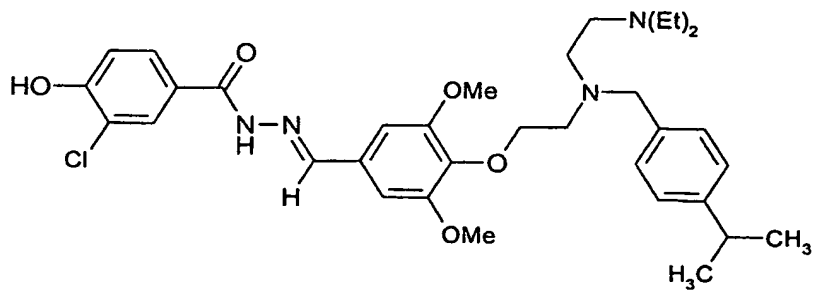


5

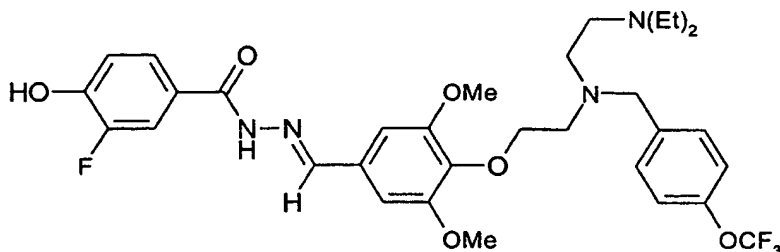
## EXAMPLE 157:



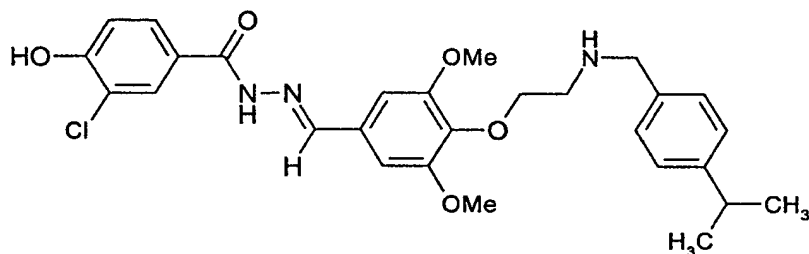
## 10 EXAMPLE 158:



## EXAMPLE 159:



## 5 EXAMPLE 160:

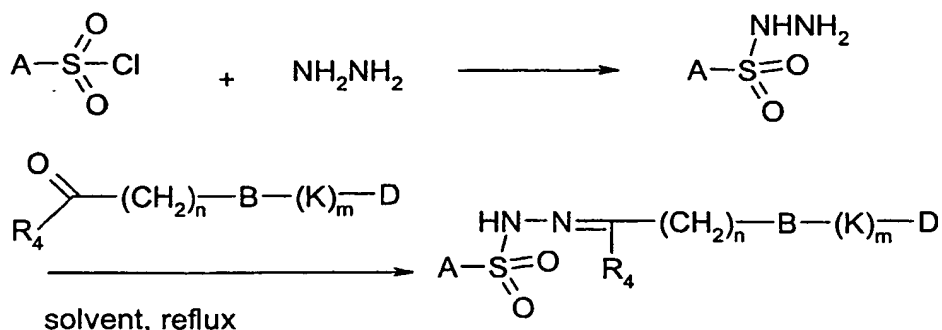


10 General procedures for the preparation of alkylidene arylsulfonyl hydrazides according to the invention

The compounds of general formula I are prepared according to one embodiment of the invention, the alkylidene arylsulfonyl hydrazides of general formula III, that is, by converting an arylsulfonyl halide, for example chloride or bromide to the corresponding hydrazide derivative and

15 further reacting the product arylsulfonyl hydrazide compound with a substituted aldehydes or ketones to yield alkylidene arylsulfonyl hydrazide derivatives as illustrated in Scheme IV.

SCHEME IV



wherein A, B, K, D, m, n and R<sup>4</sup> are as defined for formula I.

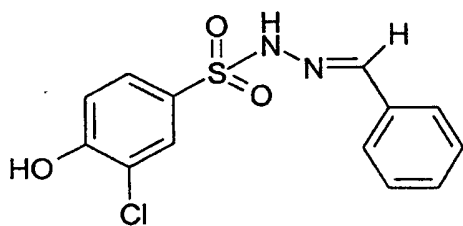
- 5 The synthesis of the arylsulfonylhydrazide precursors is performed by application of general methodology, for example as described by Friedman, L.; Little, R.L; Reichle, W. R. in *Org. Synth. Coll. Vol. V*, 1973, 1055-1057, by slowly adding the arylsulfonyl chloride either neat, or in a solution in an inert solvent such as tetrahydrofuran, dimethyl ether, dioxane or diethyl ether to an excess of hydrazine, either neat or in solution in the one of the above solvents or a mixture of these at -20°C to 100°C, preferably between 0°C to 60°C. When the reaction is judged to be completed, the excess of solvent and volatile reagents is removed by distillation either at atmospheric pressure or *in vacuo*. The residual product can be further purified by recrystallization from a solvent such as methyl alcohol, ethyl alcohol, isopropyl alcohol, water, toluene, acetic acid, dioxane, tetrahydrofuran or a mixture of two or more of the above solvents when compatible.

Alternatively, the product can be purified by column chromatography using dichloromethane/-methanol or chloroform/methanol or isopropyl alcohol as eluent. The corresponding fractions are concentrated either at atmospheric pressure or *in vacuo* to provide the pure arylsulfonyl hydrazide.

By use of the above methodology the following compounds can be prepared:

#### EXAMPLE 161:

- 25 3-Chloro-4-hydroxybenzenesulfonic acid (benzylidene)hydrazide



3-Chloro-4-hydroxybenzenesulfonyl hydrazide:

A solution of 4.82 g (21.2 mmol) 3-chloro-4-hydroxy-benzenesulfonyl chloride, (prepared according to the procedure described by Popoff, I. C.; Frank, J. R.; Whitaker R. L.; Miller H. J., Demaree K. D. *J. Agr. Food Chem.* 1969, 17, 810.) in 15 ml THF was added dropwise with stirring to 3.4 ml 50% hydrazine hydrate (54.4 mmol, 2.5 eq.) at such a rate that the temperature is maintained below 10°C. A precipitate formed after the addition was completed. The mixture was stirred for an additional 30 min, and cooled to 0°C. The solid was collected in a Büchner funnel, washed several times with distilled water, and air dried. Recrystallization from methanol provided 1.20 g 3-chloro-4-hydroxybenzenesulfonyl hydrazide as a white solid.

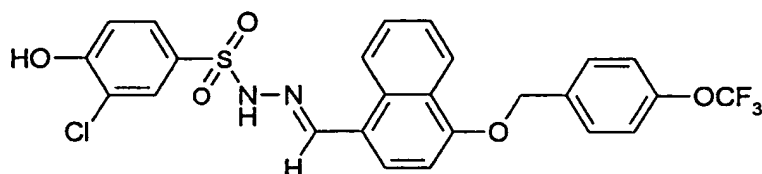
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.78 (bs, 4 H), 6.72 (d, J = 8.6 Hz, 1 H), 7.35 (dd, J = 2.3, 8.6 Hz, 1 H), 5.55 (J = 2.2 Hz, 1 H); MS(Cl): m/z 223, 221.

To a solution of 105 mg (0.48 mmol) of the above 3-chloro-4-hydroxybenzenesulfonyl hydrazide in 5 ml methanol was added 0.05 ml (52 mg, 0.49 mmol) benzaldehyde and one drop of acetic acid. After 30 min the mixture was concentrated. Flash chromatography (silica gel, 2:1 hexane/ethylacetate) provided 67 mg (45%) of the title compound as a solid.

<sup>1</sup>H (DMSO-d<sub>6</sub>): δ 7.10 (d, J = 8.6 Hz, 1 H), 7.38 (m, 3 H), 7.55 (dd, J = 2.3, 6.0 Hz, 2 H), 7.66 (d, J = 2.2, 8.6 Hz, 1 H), 7.76 (d, J = 2.2 Hz, 1 H), 7.90 (s, 1 H), 11.3 (m, 2 H). MS(Cl): m/z 311.

EXAMPLE 162:

3-Chloro-4-hydroxy-benzenesulfonic acid [4-(4-trifluoromethoxybenzyloxy)-1-naphthylmethylene]hydrazide



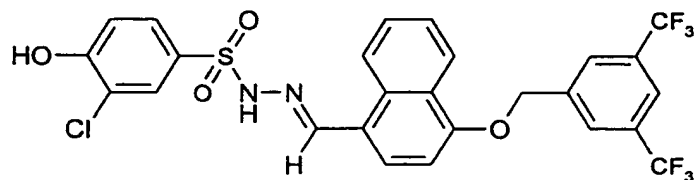
- 5 To a solution of 3-chloro-4-hydroxy-benzene sulfonyl hydrazide (105 mg, 0.48 mmol) in 5 ml methanol was added 4-trifluoromethoxybenzyloxy-1-naphthaldehyde (163 mg, 0.49 mmol) and a catalytical amount of glacial acetic acid (5 drops). The reaction mixture was stirred overnight, and filtered. The filtrate was concentrated under vacuo to give the crude product. Flash chromatography (silica gel, 1:1 hexane/ethylacetate) provided 145 mg (56%) of the title compound as a solid.
- 10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 5.27 (s, 2 H), 6.06 (s, 1 H), 6.83 (d, J = 8.1 Hz, 1 H), 7.10 (d, J = 8.1 Hz, 1 H), 7.26 (d, J = 7.3 Hz, 2 H), 7.50 - 7.60 (m, 5 H), 7.80 (s, 1 H), 7.85 (dd, J = 3.0, 8.2 Hz, 1 H), 8.08 (d, J = 2.1 Hz, 1 H), 8.26 (s, 1 H), 8.36 (d, J = 7.76 Hz, 1 H), 8.67 (d, J = 8.5 Hz, 1 H).

- 15 CIMS m/z: 551, 553.

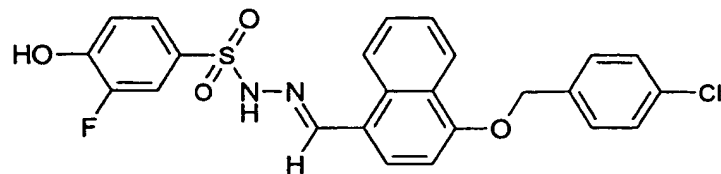
By using the above methodology, the following compounds may be prepared:

EXAMPLE 163:

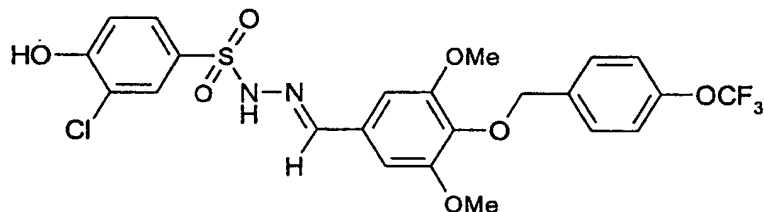


20

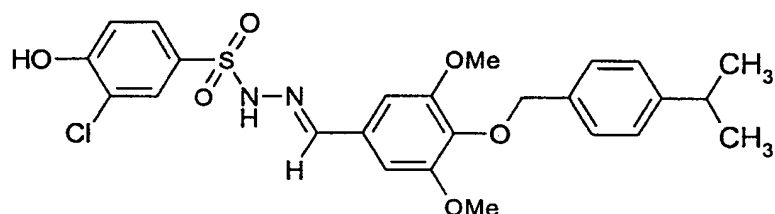
EXAMPLE 164:



## EXAMPLE 165:



## EXAMPLE 166:



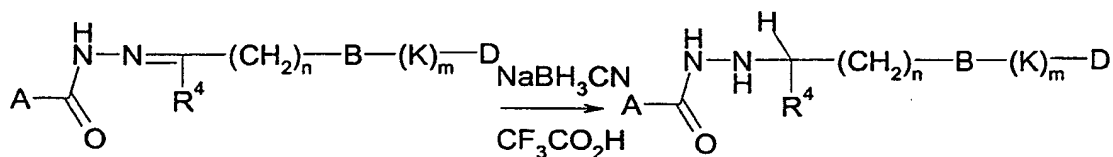
5

Synthesis of alkylhydrazides according to the invention:

The alkylidene hydrazide derivatives given above can be reduced to the dihydroderivatives by the method given in Scheme V:

10

## SCHEME V



15

where A, R<sup>4</sup>, B, K, D, m and n are as defined for formula I.

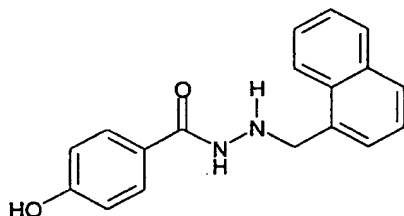
The alkylhydrazide derivatives can be prepared by reduction (i.e. Lane, C.F.(1975), Synthesis, p.135) of the corresponding alkylidene hydrazides using a metal hydride, such as sodium borohydride or sodium cyanoborohydride. The alkylidene hydrazide derivative is treated with between 1-10 equivalents, preferentially 1-3 equivalents, of sodium cyanoborohydride in a solvent such as methyl alcohol, ethyl alcohol, isopropyl alcohol, tetrahydrofuran, dioxane, water or

20

a compatible mixture of two or more solvents. Optionally a small amount of an acid is used as  
5 a catalyst such as hydrochloric acid, trifluoroacetic acid, acetic acid, or sulfuric acid. The reactions are performed at 0°C to 60°C, preferably at 10°C to 30°C. When the reaction is complete as judged by HPLC or TLC (silica gel, 1% methanol in dichloromethane as eluent) the solvent(s) are removed and the residue is chromatographed on a silica gel column using 1% methanol in dichloromethane or chloroform as an eluent. The corresponding fractions are concentrated to give the desired product. Specific examples illustrating the preparation of alkylhydrazides according to the invention are provided below.

EXAMPLE 167:

15 4-hydroxybenzoic acid (1-naphthylmethyl)hydrazide

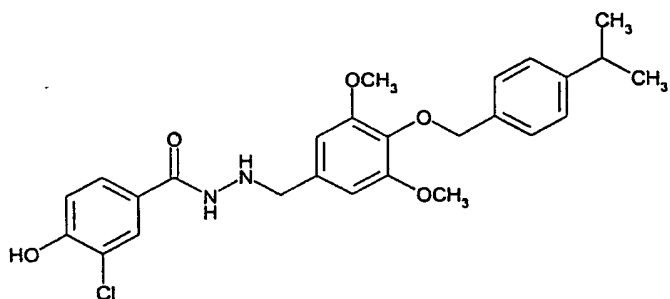


4-Hydroxybenzoic acid (1-naphthylmethylene)hydrazide (100 mg, 0.34 mmol) was dissolved in methanol (10 mL) and treated with sodium cyanoborohydride (236 mg, 4.1 mmol) followed by two drops of trifluoroacetic acid. After stirring the reaction solution for three hours at room  
20 temperature, the solvent was evaporated in vacuo. The residue was introduced into a silica gel column and eluted with dichloromethane/methanol (99/1). Evaporation of the corresponding fractions in vacuo gave the title compound in 30% yield. MS (ESI) m/z 293 (M+H)<sup>+</sup>.

Using the same methodology as described above the following compound was prepared:  
25

EXAMPLE 168:

3-Chloro-4-hydroxybenzoic acid N-[4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzyl]hydrazide

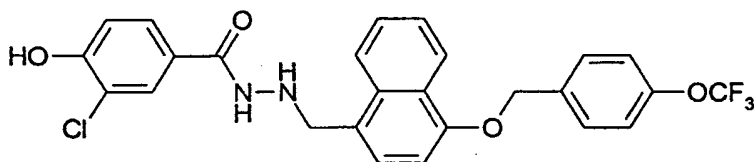


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.18 (d, 6H), 2.87 (m, 1H), 3.75 (s, 6H), 3.90 (m, 2H), 4.80 (s, 2H), 5.43 (brd s, 1H), 6.68 (s, 2H), 6.98 (d, 1H), 7.20 (d, 2H), 7.34 (d, 2H), 7.64 (dd, 1H), 7.87 (d, 1H), 9.89 (brd s, 1H), 10.80 (s, 1H); MS (APCI): 485.2.

5

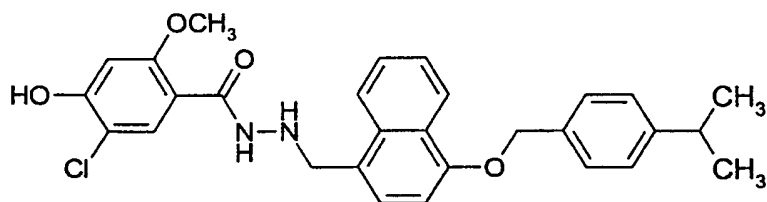
Furthermore, the following compounds may also be prepared:

EXAMPLE 169:

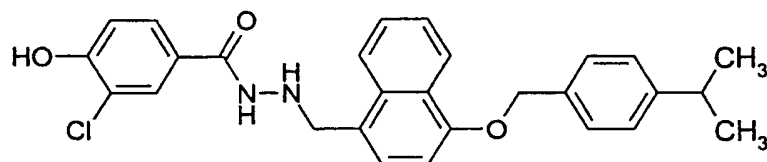


10

EXAMPLE 170:

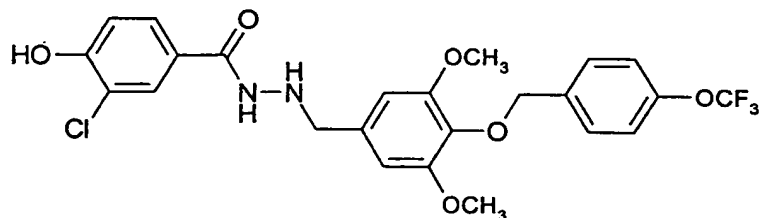


EXAMPLE 171:

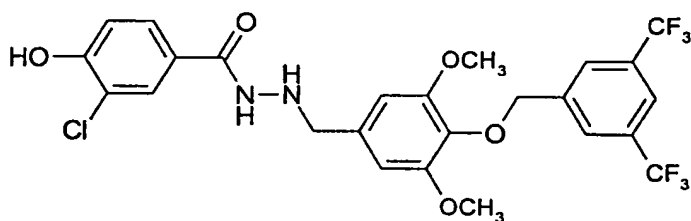
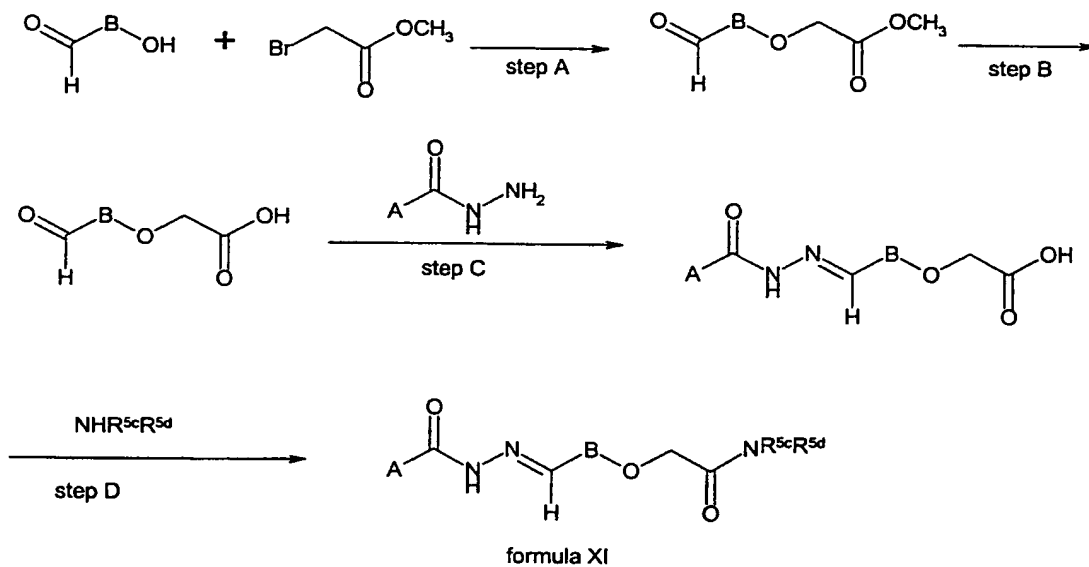


15

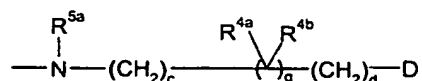
## EXAMPLE 172:



## EXAMPLE 173:

5 General procedure for synthesis of compounds of the general formula XI:

A and B are as defined for formula I and  $-NR^{5c}R^{5d}$  is



where  $R^{5a}$ ,  $R^{4a}$ ,  $R^{4b}$ , c, q, d and D are as defined for for-

10

mula I or

-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

Step A: The reaction is known and is generally performed by stirring hydroxy benzaldehyde, hydroxy naphthaldehyde or the like together with a bromo acetic acid ester (either methyl, ethyl or other lower alkyl ester) in the presence of a base such as lithium, sodium, potassium or cesium carbonate in a solvent such as acetone, 2-methyl-3-pentanone, tetrahydrofuran, dioxane, DMSO, DMF, ethylene glycol, benzene, toluene or a mixture of the above solvents. The reactions are performed between 0°C to 130°C, preferably between 20°C to 100°C, most preferably at or about the reflux temperature of the solvent. The reactions are preferably conducted under an inert atmosphere such as N<sub>2</sub> or Ar. When the reaction is complete as judged by disappearance of the starting ester by TLC or HPLC, the solvent may be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent.

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Step B: The resulting derivative of acetic ester is then saponified using methods well-known to those skilled in the art such as dissolving the compound in an appropriate solvent such as a lower alcohol (e.g methanol, ethanol or isopropanol), DMF, dioxane or DMSO and adding an aqueous base like lithium, sodium or potassium hydroxide. The reactions are performed between 0°C to 130°C, preferably between 20°C to 100°C. When the reaction is complete as judged by disappearance of the starting ester by TLC or HPLC, the solvent may be removed by concentration at atmospheric or reduced pressure. The product can then be isolated by pouring the residue into water or cooled water and acidifying the mixture using an inorganic acid such as hydrochloric acid or sulfuric acid. The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent .

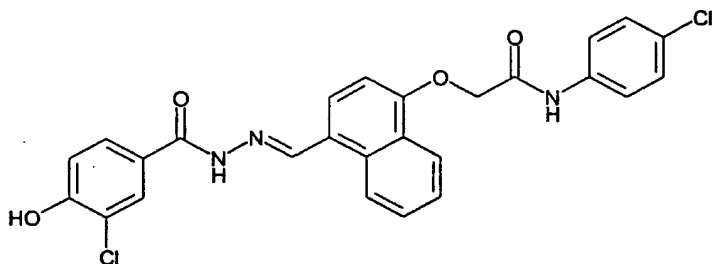
30

- Step C: The resulting carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N<sub>2</sub> or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further re-crystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.
- Step D: The resulting acid is then coupled to a primary or secondary amine using one of the methods well-known to those skilled in the art. This coupling can be performed using one of the standard amide or peptide synthesis procedures such as by generating an active ester, an anhydride or an acid halide that can then react with the amine to give a compound of formula XI. Step D can also be done combinatorially with a selected number of amines. The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent giving a compound of formula XI.

- Specific examples illustrating the preparation of compounds of the general formula XI according to the invention are provided below.

## EXAMPLE 174:

2-{4-[(3-Chloro-4-hydroxy-benzoyl)hydrazonomethyl]naphthyl-1-yloxy}-N-(4-chloro-phenyl)acetamide



Step A: Hydroxynaphthaldehyde (10 g, 58 mmol), potassium carbonate (16 g, 110 mmol), and methyl bromoacetate (16 g, 100 mmol) were refluxed in acetone (120 mL) overnight. The reaction mixture was poured into an Erlenmeyer flask containing approximately 500 mL of ice chips. The mixture was stirred until all of the ice was melted. (4-Formylnaphth-1-yloxy) acetic acid methyl ester (13 g, 50 mmol) was filtered and dried in vacuo overnight.

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.86 (s, 3H), 4.93 (s, 2H), 6.80 (d, 1H), 7.61 (t, 1H), 7.72 (t, 1H), 7.90 (d, 1H), 8.42 (d, 1H), 9.29 (d, 1H), 10.22 (s, 1H).

Step B: The above ester (13 g, 50 mmol) was dissolved in methanol (100 mL) and 2 M NaOH (40 mL) was added. The reaction solution was stirred overnight and concentrated to approximately 100 mL under vacuo. The residue was poured into approximately 500 mL of ice chips and the mixture was acidified (by pH paper) with the addition of 3N HCl. The mixture was stirred until all of the ice was melted. (4-Formylnaphth-1-yloxy) acetic acid was filtered and washed with water.

15

20

Step C: To a solution of 3-chloro-4-hydroxybenzoic acid hydrazide (2g, 10.7 mmol) in DMSO (20 mL) was added the above (4-formylnaphth-1-yloxy) acetic acid (3g, 13 mmol) and a catalytic amount of acetic acid (10 drops). The solution was stirred overnight and diluted with ethyl acetate. The solution was washed with water (3x), brine, and dried over  $\text{MgSO}_4$ . The volume was reduced to approximately 100 mL and placed in an ice-bath. The resulting solid was filtered and washed with cold ethyl acetate to afford {4-[(3-chloro-4-hydroxy-benzoyl)hydrazonomethyl]naphth-1-yloxy} acetic acid.

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$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.91 (s, 2H), 6.95 (d, 1H), 7.02 (d, 1H), 7.55 (t, 1H), 7.64 (t, 1H), 7.74 (d, 1H), 7.92 (d, 1H), 8.27 (d, 1H), 8.90 (m, 2H), 10.92 (brd s, 1H), 11.63 (s, 1H), 13.14 (brd s, 1H).

5

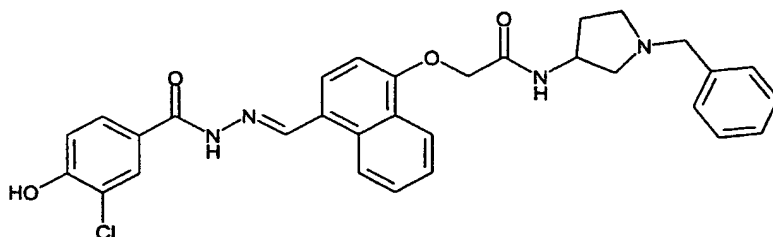
Step D: To a solution of the hydrazone-carboxylic acid (50 mmol) in anhydrous DMSO was added a solution of carbonyldiimidazole (55 mmol) in anhydrous DMSO. After the evolution of gases ceased (approximately 3–4 minutes), the amine was added and the reaction mixture was stirred for 3 hours. The mixture was diluted with ethyl acetate and washed with water, 10 brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the crude material, which was purified by reverse phase HPLC chromatography to give the title compound.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.99 (s, 2H), 7.04 (m, 2H), 7.36 (d, 2H), 7.65 (m, 4H), 7.79 (t, 2H), 15 7.99 (s, 1H), 8.40 (d, 1H), 8.72 (s, 1H), 8.92 (d, 1H), 10.42 (s, 1H), 10.96 (s, 1H), 11.69 (s, 1H); MS (APCI): 507.9.

By using the same methodology, the following compounds were prepared:

20 EXAMPLE 175:

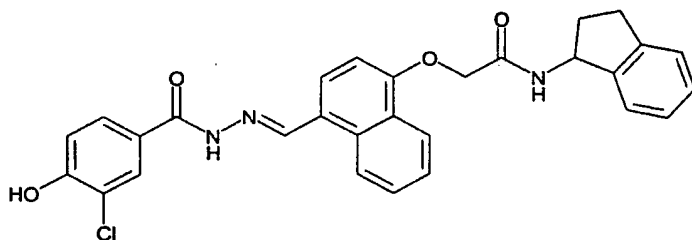
N-(1-Benzylpyrrolidin-3-yl)-2-{4-[(3-chloro-4-hydroxy-benzoyl)hydrazonomethyl]naphth-1-yloxy}acetamide



$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  1.96 (m, 2H), 2.32 (m, 5H), 4.58 (s, 2H), 6.78 (d, 1H), 6.92 (d, 1H), 7.15 (m, 5H), 7.47 (t, 1H), 7.52 (t, 1H), 7.62 (d, 2H), 7.82 (d, 1H), 8.18 (m, 2H), 8.78 (d, 2H), 10.75 (brd s, 1H), 11.52 (s, 1H); MS (APCI): 556.9.

5 EXAMPLE 176:

2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}-N-indan-1-yl-acetamide

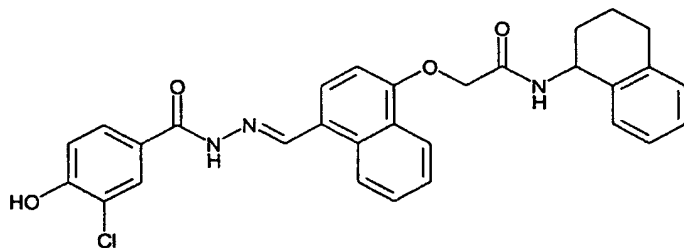


10  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  1.94 (m, 1H), 2.40 (m, 1H), 2.80-3.07 (m, 3H), 4.87 (s, 2H), 7.04 (d, 1H), 7.10 (d, 1H), 7.21 (m, 4H), 7.61 (t, 1H), 7.69 (t, 1H), 7.80 (t, 2H), 8.10 (s, 1H), 8.42 (d, 1H), 8.64 (d, 1H), 8.98 (m, 2H), 11.00 (brd s, 1H), 11.68 (s, 1H); MS (APCI): 514, 516.

EXAMPLE 177:

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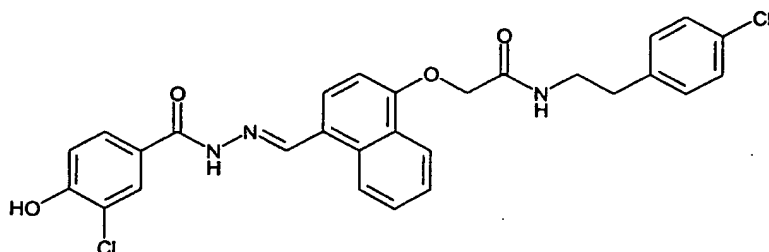
2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}-N-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide



20  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  1.75 (m, 2H), 1.92 (m, 2H), 2.74 (m, 2H), 4.87 (m, 2H), 5.12 (m, 1H), 7.12 (m, 6H), 7.61 (t, 1H), 7.74 (t, 1H), 7.84 (m, 2H), 8.01 (s, 1H), 8.40 (d, 1H), 8.62 (d, 1H), 8.97 (m, 2H), 11.72 (s, 1H); MS (APCI): 528, 530.

## EXAMPLE 178:

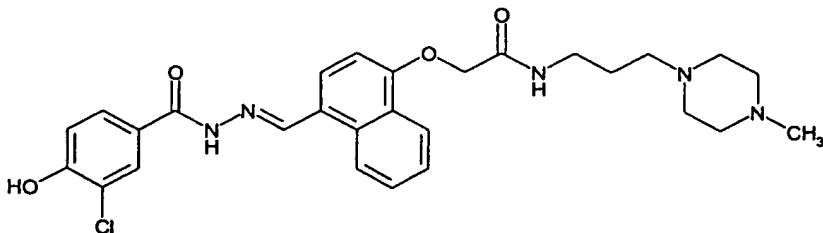
2-[4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy]-N-[2-(4-chloro-phenyl)ethyl]acetamide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.40 (t, 2H), 2.79 (t, 2H), 4.74 (s, 2H), 6.96 (d, 1H), 7.10 (d, 1H), 7.63 (t, 1H), 7.69 (t, 1H), 7.72 (m, 2H), 7.81 (s, 1H), 8.01 (m, 2H), 8.23 (t, 1H), 8.40 (d, 1H), 8.95 (s, 1H), 9.01 (d, 1H), 10.98 (brd s, 1H), 11.70 (s, 1H); MS (APCI) 538.8, 537.8.

## EXAMPLE 179:

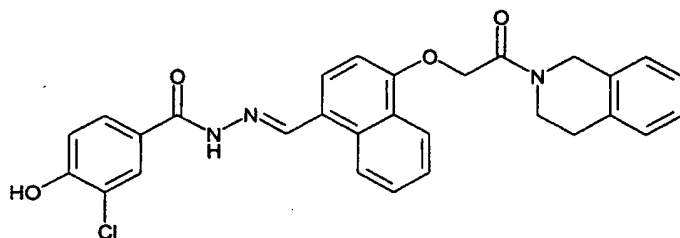
2-[4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy]-N-[3-(4-methylpiperazin-1-yl)propyl]acetamide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.50 (m, 2H), 2.26 (m, 2H), 2.48 (m, 5H), 3.01 (m, 8H), 4.53 (s, 2H), 6.78 (d, 1H), 6.89 (d, 1H), 7.38 (t, 1H), 7.47 (t, 1H), 7.5 (t, 2H), 7.76 (d, 1H), 8.01 (t, 1H), 8.22 (d, 1H), 8.68 (d, 1H), 8.74 (s, 1H), 10.74 (brd s, 1H), 11.45 (s, 1H); MS (APCI): 538.0.

## EXAMPLE 180:

3-Chloro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2-oxoethoxy]naphth-1-ylmethylene}hydrazide

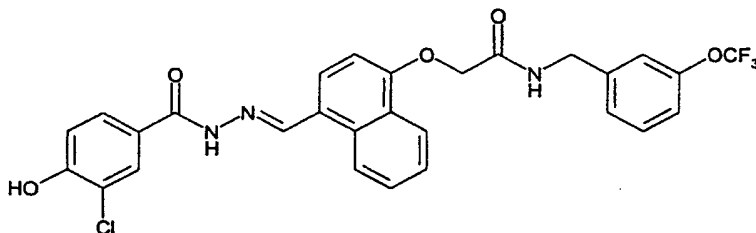


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.90 (d, 2H), 2.75 (m, 2H), 4.70 (d, 2H), 5.24 (s, 2H), 6.90 (t, 2H), 7.10 (m, 4H), 7.66 (m, 4H), 8.01 (s, 1H), 8.34 (t, 1H), 8.95 (m, 2H), 10.97 (brd s, 1H), 11.68 (brd s, 1H); MS (APCI): 514.2.

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## EXAMPLE 181:

2-{4-[(3-Chloro-4-hydroxy-benzoyl)hydrazonomethyl]naphth-1-yloxy}-N-(3-trifluoromethoxybenzyl)acetamide

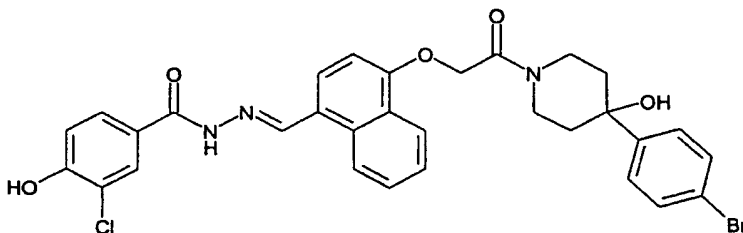


10

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.49 (d, 2H), 4.90 (s, 2H), 7.13 (m, 2H), 7.42 (m, 4H), 7.59 (dd, 1H), 7.68 (dd, 1H), 7.78 (m, 2H), 8.03 (s, 1H), 8.51 (d, 1H), 8.79 (t, 1H), 9.0 (m, 2H), 10.85 (brd s, 1H), 11.72 (s, 1H); MS (APCI): 572.1.

## 15 EXAMPLE 182:

3-Chloro-4-hydroxybenzoic acid (4-{2-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-2-oxoethoxy}naphth-1-ylmethylene)hydrazide

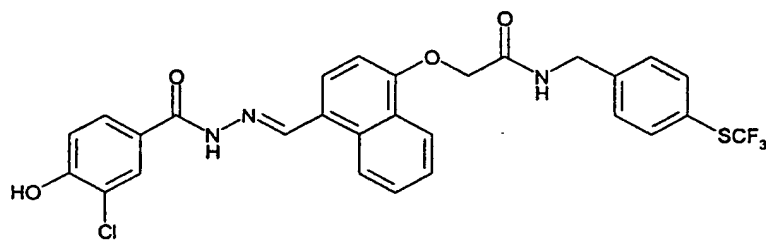


MS (APCI): 636, 638.

EXAMPLE 183:

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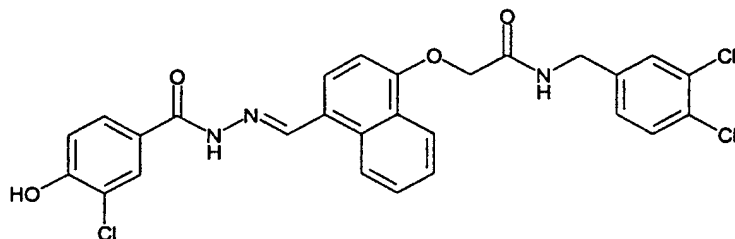
2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}-N-(4-trifluoromethylsulfanylbenzyl)acetamide



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.48 (d, 2H), 4.88 (s, 2H), 7.08 (m, 2H), 7.45 (d, 2H), 7.68 (m, 4H),  
10 7.82 (m, 2H), 8.01 (d, 1H), 8.52 (d, 1H), 8.87 (t, 1H), 8.96 (s, 1H), 9.01 (d, 1H), 10.98 (brd s,  
1H), 11.72 (s, 1H); MS (APCI): 588.2

## EXAMPLE 184:

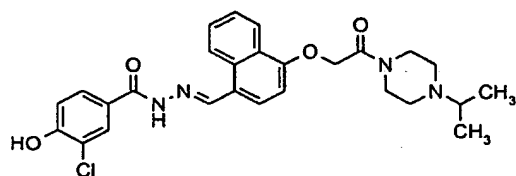
2-[4-[(3-Chloro-4-hydroxy-benzoyl)hydrazonomethyl]naphth-1-yloxy]-N-(3,4-dichlorobenzyl)acetamide



5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.42 (d, 2H), 4.91 (s, 2H), 7.08 (d, 1H), 7.11 (d, 1H), 7.22 (d, 1H), 7.48 - 7.76 (m, 4H), 7.82 (d, 2H), 8.04 (d, 1H), 8.51 (dd, 1H), 8.83 (m, 1H), 8.91 (s, 1H), 10.02 (d, 1H), 11.00 (brd s, 1H), 11.73 (s, 1H); MS (APCI): 556.0

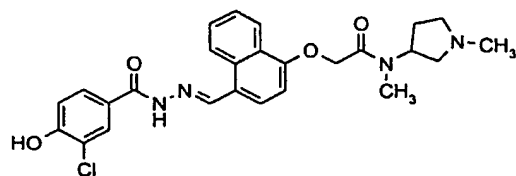
## 10 EXAMPLE 185:



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$^1\text{H}$  NMR (DMSO- $D_6$ ):  $\delta$  0.97 (d, 6H), 2.42 (m, 2H), 2.50 (m, 2H), 2.68 (septet, 1H), 3.49 (m, 4H), 5.12 (s, 2H), 7.03 (d, 1H), 7.08 (d, 1H), 7.60 (t, 1H), 7.68 (t, 1H), 7.80 (d, 2H), 8.01 (d, 1H), 8.33 (d, 1H), 8.94 (s, 1H), 9.00 (d, 1H), 11.68 (s, 1H); MS (APCI, neg.): 507.1, 509.1.

## EXAMPLE 186:

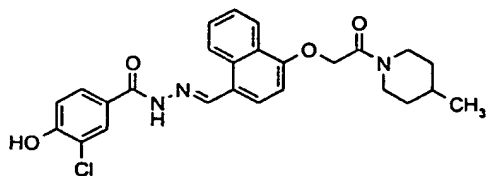


20

$^1\text{H}$  NMR (DMSO- $D_6$ ):  $\delta$  1.75 (m, 2H), 2.25 (m, 2H), 2.24 (d, 3H), 2.39 (quintet, 1H), 3.26 (m, 2H), [2.84 (s, 1.5H) + 3.04 (s, 1.5H), 3H], 5.16 (d, 2H), 6.72 (t, 1H), 7.07 (d, 1H), 7.62 (t, 1H),

7.68 (t, 1H), 7.78 (dd, 2H), 8.00 (d, 1H), 8.34 (m, 1H), 8.94 (s, 1H), 9.00 (d, 1H), 11.65 (brd s, 1H); MS (APCI): 495.2, 497.2.

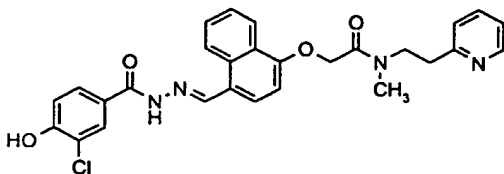
EXAMPLE 187:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 0.86 (s, 3H), 1.48 (m, 4H), 2.38 (t, 1H), 2.72 (m, 1H), 3.09 (t, 1H), 3.84 (t, 1H), 4.18 (t, 1H), 5.09 (m, 2H), 7.03 (d, 1H), 7.11 (d, 1H), 7.59 (t, 1H), 7.64 (t, 1H), 7.82 (d, 2H), 8.01 (s, 1H), 8.33 (d, 1H), 8.94 (s, 1H), 9.00 (d, 1H), 11.0 (brd s, 1H), 11.69 (brd s, 1H); MS (APCI): 480.1, 482.1.

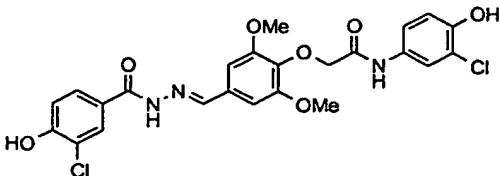
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EXAMPLE 188:



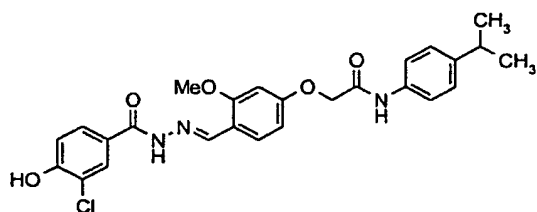
15 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.88 (s, 1.5H) + (s, 1.5H), 3H], 2.95 (t, 1H), 3.01 (s, 1.5H), 3.10 (s, 1.5H), 3.10 (t, 1H), 3.69 (t, 1H), 3.81 (t, 1H), 5.05 (d, 2H), [6.66 + 6.95 (d), 1H], 7.10 (d, 1H), [7.20 + 7.38 (d), 1H], 7.29 (d, 1H), 7.67 (m, 5H), 8.01 (s, 1H), 8.30 (t, 1H), 8.53 (dd, 1H), 8.97 (m, 2H), 11.67 (brd s, 1H); MS (APCI): 517.3, 519.2.

20 EXAMPLE 189:



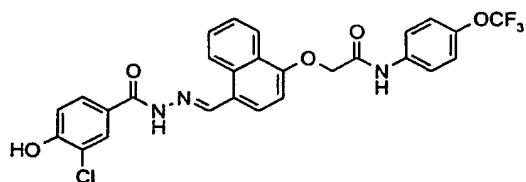
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.88 (s, 6H), 4.75 (s, 2H), 6.93 (d, 1H), 7.08 (m, 3H), 7.34 (dd, 1H), 7.74 (dd, 1H), 7.79 (d, 1H), 7.95 (s, 1H), 8.37 (s, 1H), 9.74 (s, 1H), 10.03 (m, 1H), 10.96 (brd s, 1H), 11.76 (brd s, 1H); MS (APCI): 534.4, 536.2.

5 EXAMPLE 190:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.18 (d, 6H), 2.85 (m, 1H), 3.87 (s, 3H), 4.76 (s, 2H), 6.71 (d, 1H), 6.78 (d, 1H), 7.06 (d, 1H), 7.20 (d, 2H), 7.58 (d, 2H), 7.78 (dd, 1H), 7.82 (d, 1H), 7.99 (d, 1H), 8.70 (s, 1H), 10.04 (s, 1H), 10.92 (brd s, 1H), 11.62 (brd s, 1H); MS (APCI): 496.5, 498.2.

EXAMPLE 191:



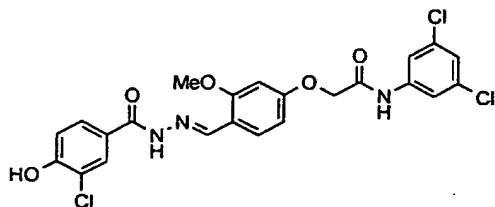
15

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 4.88 (s, 2H), 6.93 (t, 2H), 7.23 (d, 2H), 7.47 - 7.70 (m, 6H), 7.86 (d, 1H), 8.30 (d, 1H), 8.80 (s, 1H), 8.87 (d, 1H), 10.34 (s, 1H), 10.82 (brd s, 1H), 11.55 (brd s, 1H); MS (APCI): 558.5, 560.0.

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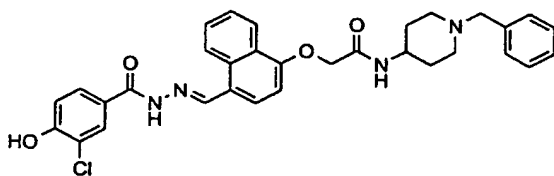
25

## EXAMPLE 192:



- 5  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ ):  $\delta$  4.06 (s, 3H), 4.94 (s, 2H), 6.81 (d, 1H), 6.89 (s, 1H), 7.19 (d, 1H), 7.45 (s, 1H), 7.90 (m, 3H), 8.10 (s, 1H), 8.82 (s, 1H), 10.62 (s, 1H), 11.07 (brd s, 1H), 11.75 (s, 1H); MS (APCI): 523.3, 524.8, 526.6.

## EXAMPLE 193:

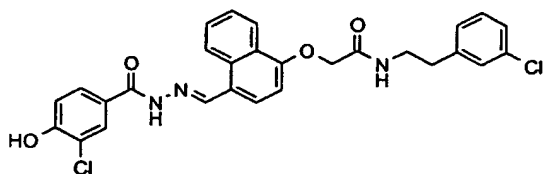


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- $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ ):  $\delta$  1.68 (m, 2H), 2.01 (m, 2H), 3.05 (m, 2H), 3.35 (m, 2H), 3.86 (m, 1H), 4.26 (s, 2H), 4.81 (s, 2H), 6.95 (d, 1H), 7.09 (d, 1H), 7.46 (s, 5H), 7.59 (m, 1H), 7.66 (t, 1H), 7.77 (d, 1H), 7.98 (d, 1H), 8.34 (d, 1H), 8.41 (d, 1H), 8.92 (m, 2H), 9.65 (brd s, 1H), 11.02 (brd s, 1H), 11.80 (brd s, 1H); MS (APCI): 571.3, 572.3, 573.3.

15

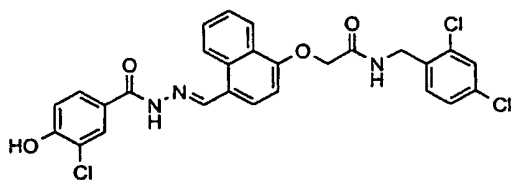
## EXAMPLE 194:



- 20  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ ):  $\delta$  2.79 (t, 2H), 3.43 (qt, 2H), 4.71 (s, 2H), 6.95 (d, 1H), 7.08 (d, 1H), 7.17 (m, 1H), 7.26 - 7.30 (m, 3H), 7.61 (t, 1H), 7.67 (t, 1H), 7.76 (m, 2H), 7.99 (d, 1H), 8.24

(t, 1H), 8.38 (d, 1H), 8.91 (s, 1H), 8.98 (d, 1H), 10.94 (s, 1H), 11.67 (s, 1H); MS (APCI): 536.3, 538.2, 539.1.

EXAMPLE 195:

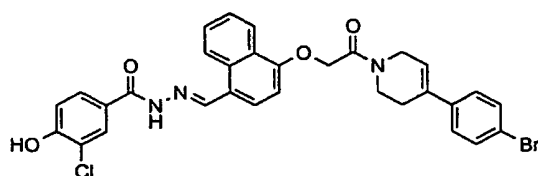


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 4.42 (d, 2H), 4.87 (s, 2H), 7.06 (m, 2H), 7.38 (d, 2H), 7.60 (t, 1H), 7.63 (m, 1H), 7.80 (t, 1H), 7.99 (d, 1H), 8.49 (d, 1H), 8.79 (t, 1H), 8.93 (s, 1H), 8.98 (d, 1H), 10.95 (s, 1H), 11.68 (s, 1H); MS (APCI): 558.2, 560.1.

10

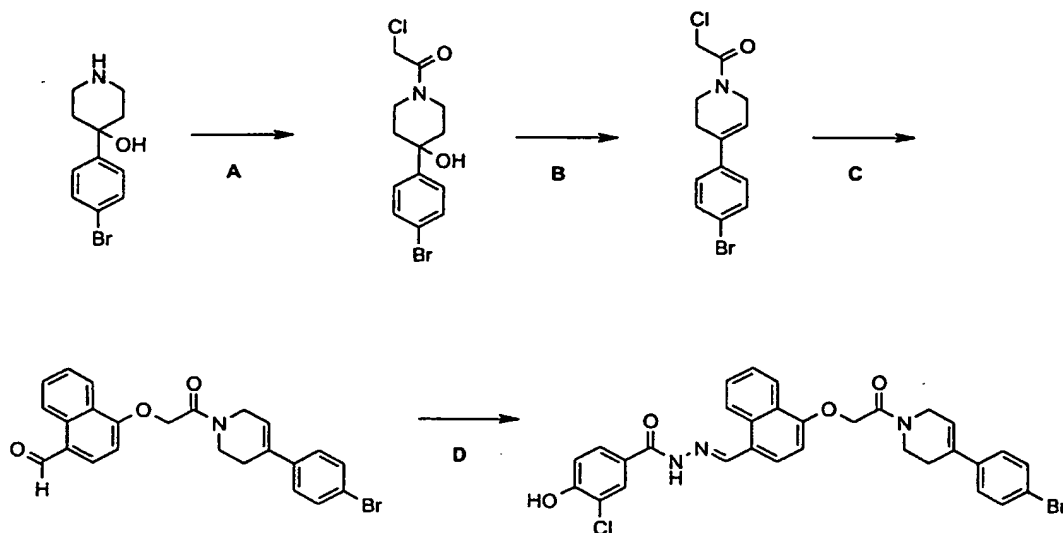
EXAMPLE 196:

15 4-(4-bromophenyl-3,4-dihydropiperidinylacetamideoxy)naphth-1-yl methylene-3-chloro-4-hydroxybenzoic acid hydrazone



20

Reaction scheme:



4-(4-bromophenyl)-4-piperidinol chloroacetamide (step A):

To a solution of 4-(4-bromophenyl)-4-piperidinol (5 g, 19.5 mmol) and diisopropylethylamine (2.8 g, 21.5 mmol) in DMF (30 mL) was added dropwise chloroacetylchloride (2.2 g, 21.5 mmol). After stirring the mixture for one hour, the mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (2x), 1 N HCl (3x), water, brine, and dried over MgSO<sub>4</sub>. The solution was concentrated and chromatographed over silica gel with ethyl acetate to give the product as a brown solid (4 g, 62 %).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.21 (d, 2H), 1.71 (t, 1H), 1.96 (t, 1H), 2.71 (t, 1H), 3.37 (t, 1H), 3.70 (d, 1H), 4.27 (d, 1H), 4.54 (s, 2H), 5.26 (s, 1H), 7.42 (d, 2H), 7.51 (d, 2H).

4-(4-bromophenyl)-3,4-dihydropiperidine chloroacetamide (step B):

To a solution of 4-(4-bromophenyl)-4-piperidinol chloroacetamide (4 g, 12 mmol) and diisopropylethylamine (4.6 mL, 26 mmol) in THF (40 mL) cooled in an ice-bath was added methanesulfonyl chloride (2 mL, 26 mmol) and the mixture was refluxed for 16 hours under a nitrogen blanket. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl (2x), aqueous NaHCO<sub>3</sub> (2x), brine (2x), and dried over MgSO<sub>4</sub>. The solvent was evaporated and the product was chromatographed over silica gel with ethyl acetate/hexane (4/6). The product was obtained as a yellow solid (1.5 g, 32%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.44 (t, 2H), 3.62 (m, 2H), 4.14 (dd, 2H), 4.42 (d, 2H), 6.21 (s, 1H), 7.36 (m, 2H), 7.51 (d, 2H).

5 4-(4-bromophenyl-3,4-dihydropiperadinylacetamideoxy)naphthaldehyde (step C):

A mixture of 4-(4-bromophenyl)-3,4-dihydropiperidine chloroacetamide (1.5 g, 4.8 mmol), 4-hydroxynaphthaldehyde (1.2 g, 7 mmol), and powdered potassium carbonate (1 g, 7.2 mmol) in acetonitrile (50 mL) was refluxed for 16 hours. The mixture was diluted with ethyl acetate and washed with brine (3x), dried over MgSO<sub>4</sub>, and concentrated. Silica gel chromatography with ethyl acetate/hexane (1/1) provided the product (1.4 g, 65%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.27-2.32 (m, 2H), 3.49-3.55 (m, 2H), 3.94 (brd s, 1H), 4.06 (brd s, 1H), 5.08 (s, 1H), 5.13 (s, 1H), 6.05 (s, 1H), 6.97 (t, 1H), 7.20 (t, 1H), 7.34 (d, 2H), 7.42-7.47 (m, 1H), 7.52-7.57 (m, 1H), 7.92 (d, 1H), 8.16 (d, 1H), 9.01 (d, 1H), 9.97 (s, 1H).

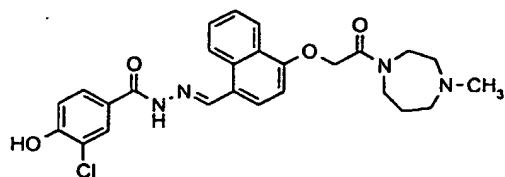
4-(4-bromophenyl-3,4-dihydropiperadinylacetamideoxy)naphth-1-yl methylene-3-chloro-4-hydroxybenzoic acid hydrazone (step D):

20 The title compound was prepared according to the general procedure for the synthesis of alkylidene hydrazides from the condensation of 3-chloro-4-hydroxybenzoic acid hydrazide and 4-(4-bromophenyl-3,4-dihydropiperadinylacetamideoxy)naphthaldehyde:

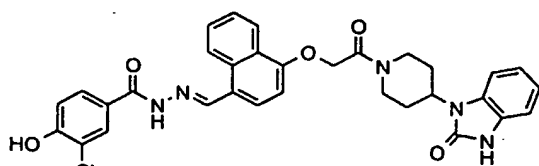
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.47-2.58 (m, 2H), 3.72 (br s, 2H), 4.13 (s, 1H), 4.26 (s, 1H), 5.14 (s, 1H), 5.18 (s, 1H), 6.23 (s, 1H), 6.50-6.53 (m, 1H), 7.03-7.06 (m, 1H), 7.35-7.38 (m, 2H), 7.52 (d, 2H), 7.58 (d, 2H), 7.59-7.67 (m, 1H), 7.75 (d, 1H), 7.84 (s, 1H), 8.32 (d, 1H), 8.89 (s, 1H), 8.92 (s, 1H), 11.41 (s, 1H); MS (APCI): 618.1, 620.1, 621.1, 622.1

245

EXAMPLE 197:

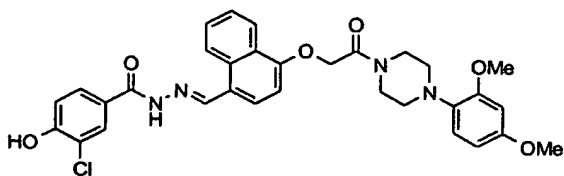


EXAMPLE 198:



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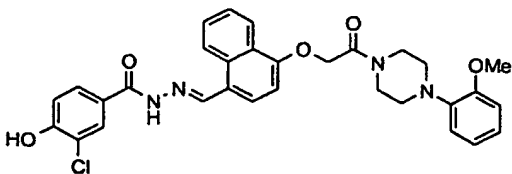
EXAMPLE 199:



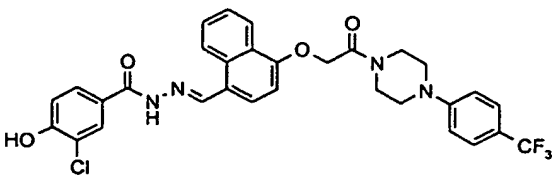
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EXAMPLE 200:

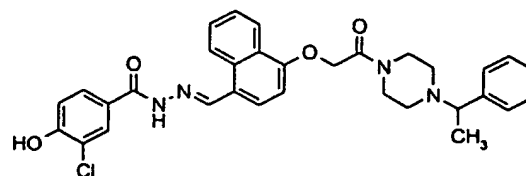


EXAMPLE 201:



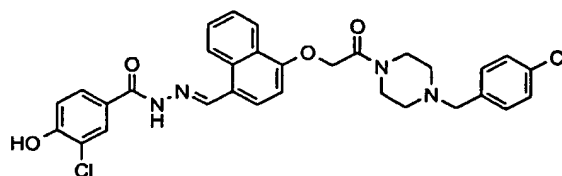
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EXAMPLE 202:

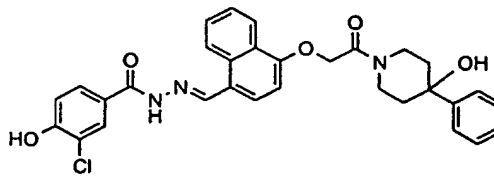


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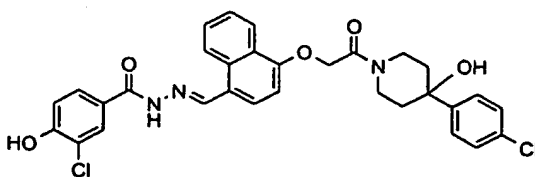
EXAMPLE 203:



EXAMPLE 204:

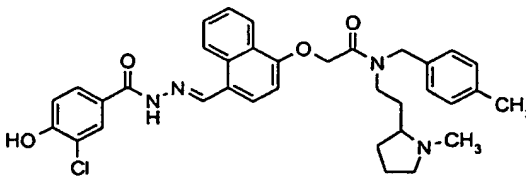


EXAMPLE 205:

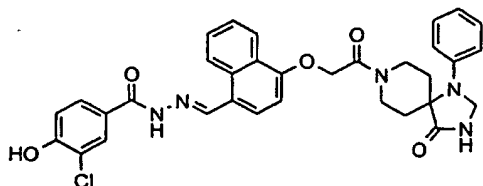


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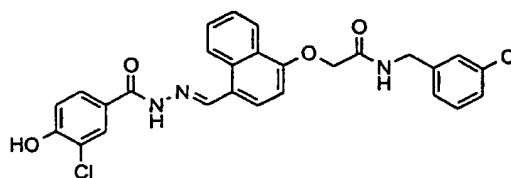
EXAMPLE 206:



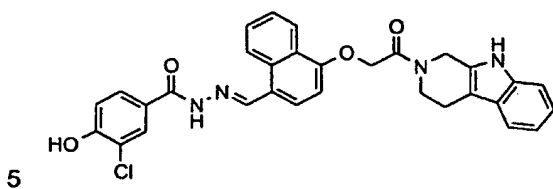
EXAMPLE 207:



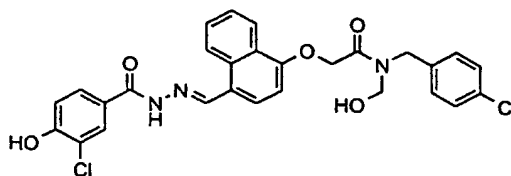
15 EXAMPLE 212:



EXAMPLE 208:

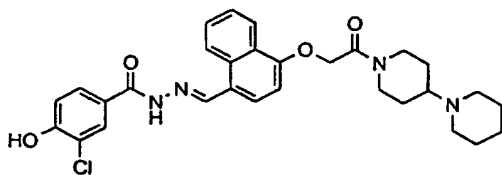


EXAMPLE 213:

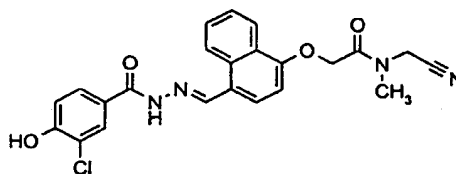


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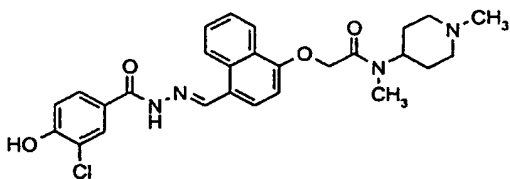
EXAMPLE 209:



EXAMPLE 214:

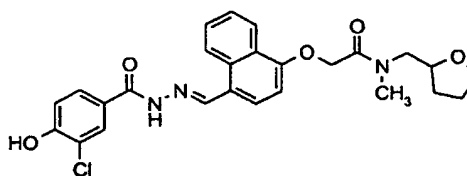


10 EXAMPLE 210:

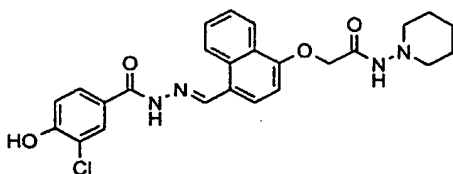


EXAMPLE 215:

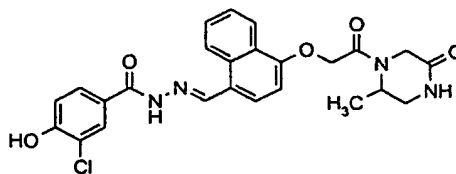
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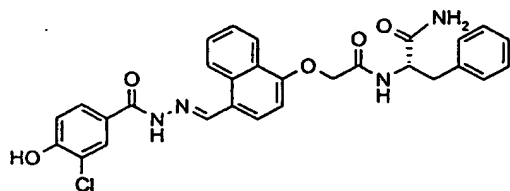
EXAMPLE 211:



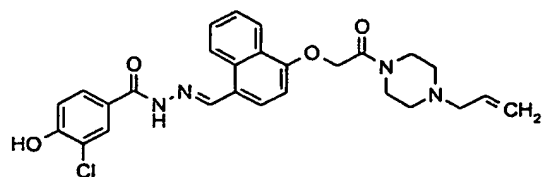
EXAMPLE 216:



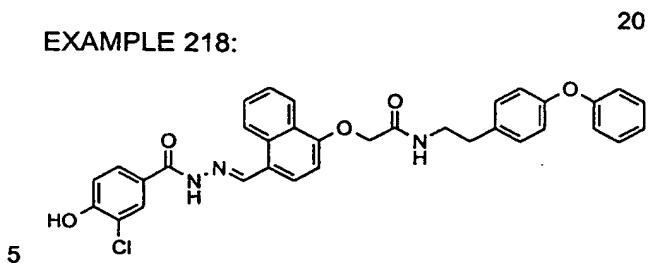
EXAMPLE 217:



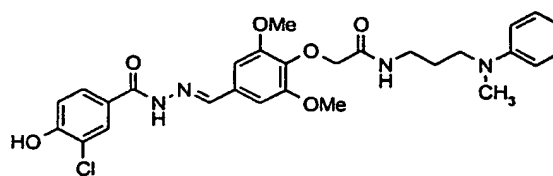
EXAMPLE 222:



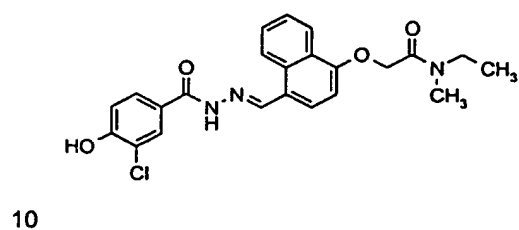
EXAMPLE 218:



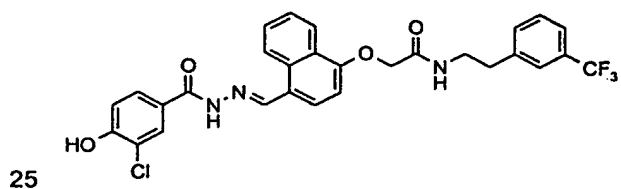
EXAMPLE 223:



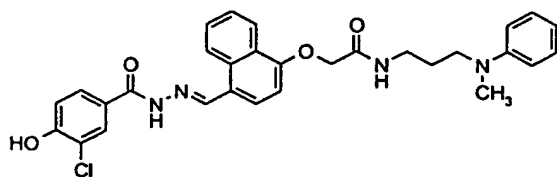
EXAMPLE 219:



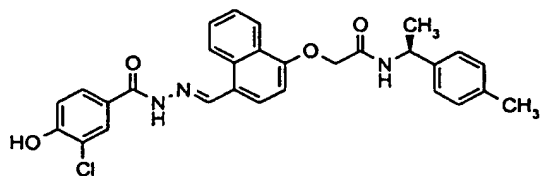
EXAMPLE 224:



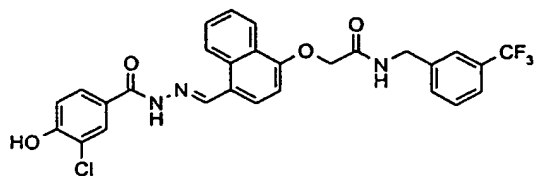
EXAMPLE 220:



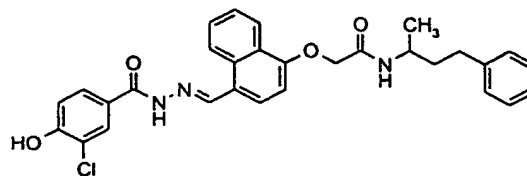
EXAMPLE 225:



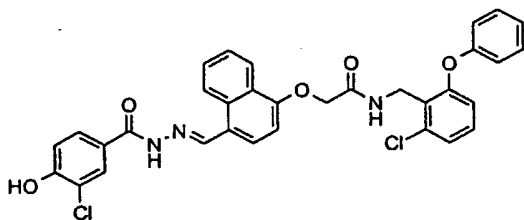
EXAMPLE 221:



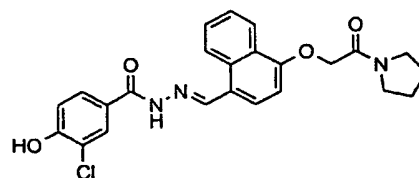
EXAMPLE 226:



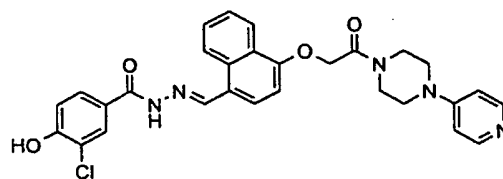
EXAMPLE 227:



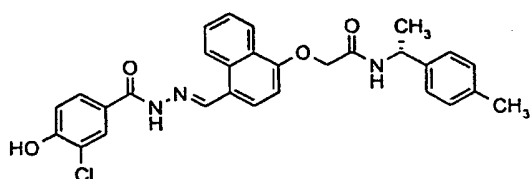
EXAMPLE 232:



EXAMPLE 233:

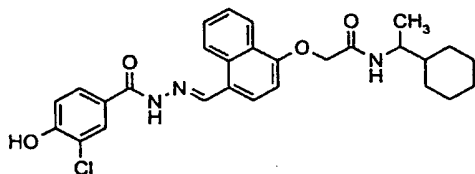


5 EXAMPLE 228:



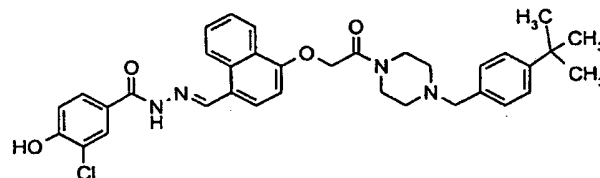
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EXAMPLE 229:



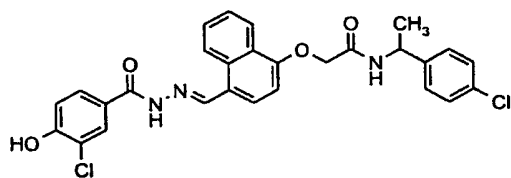
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EXAMPLE 234:

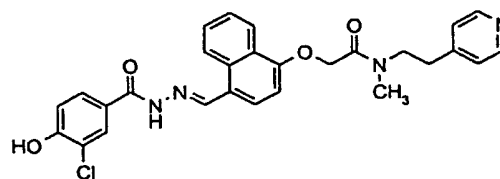


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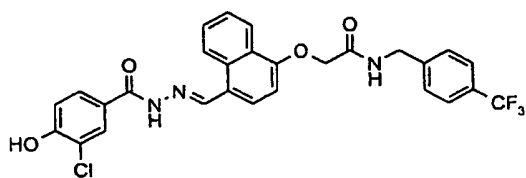
EXAMPLE 230:



EXAMPLE 235:

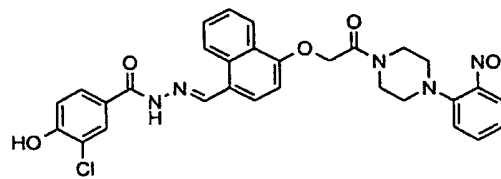


EXAMPLE 231:



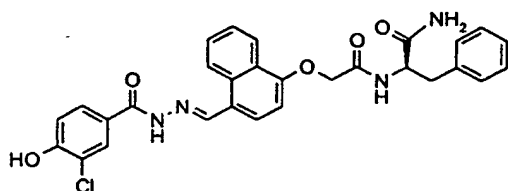
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EXAMPLE 236:

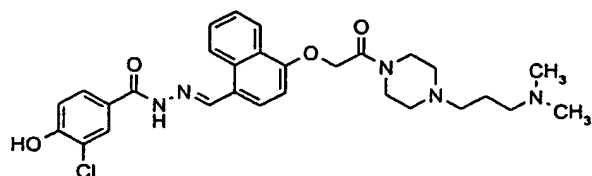


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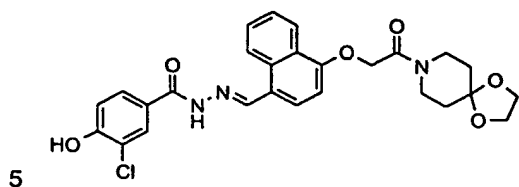
EXAMPLE 237:



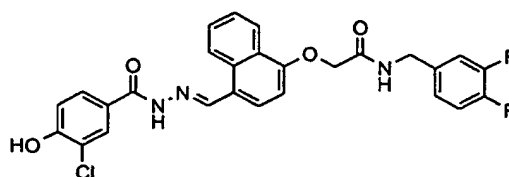
EXAMPLE 242:



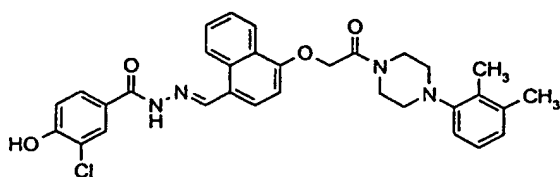
EXAMPLE 238:



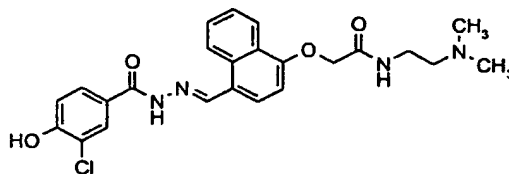
20 EXAMPLE 243:



EXAMPLE 239:



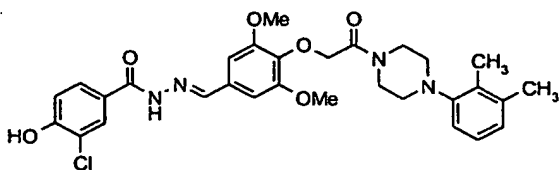
EXAMPLE 244:



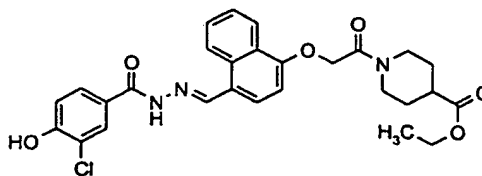
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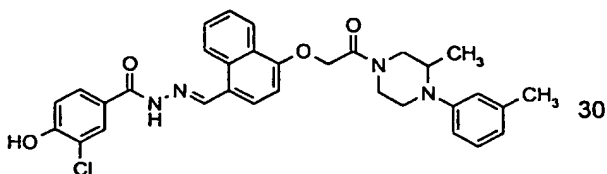
EXAMPLE 240:



EXAMPLE 245:

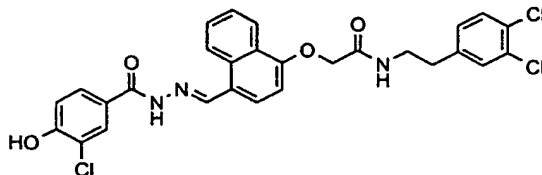


15 EXAMPLE 241:

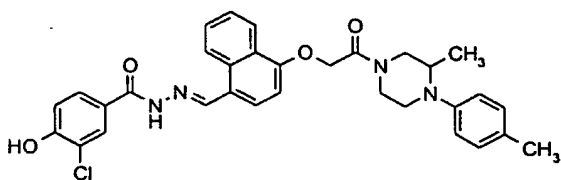


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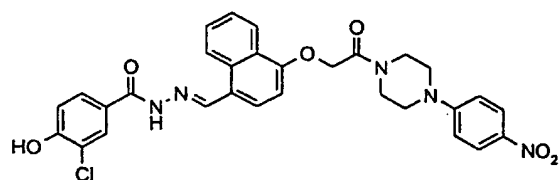
EXAMPLE 246:



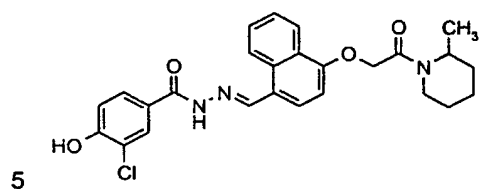
EXAMPLE 247:



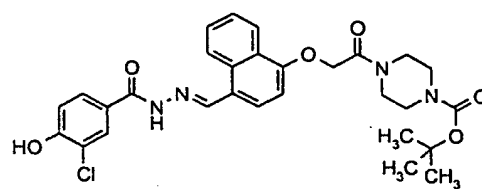
15 EXAMPLE 252:



EXAMPLE 248:

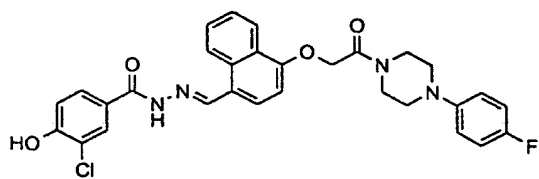


EXAMPLE 253:

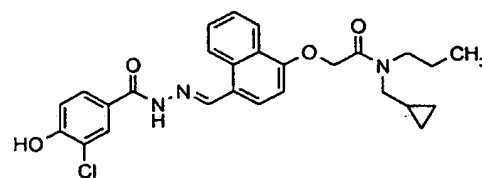


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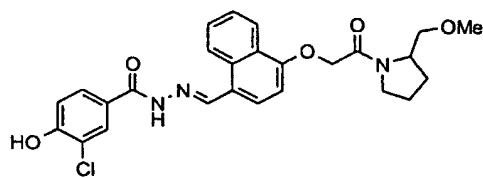
EXAMPLE 249:



EXAMPLE 254:

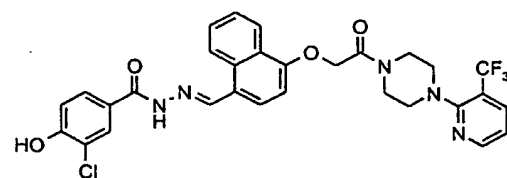


10 EXAMPLE 250:

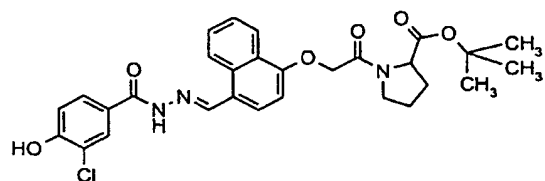


EXAMPLE 255:

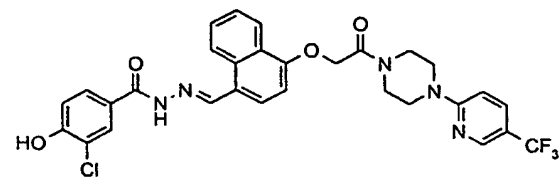
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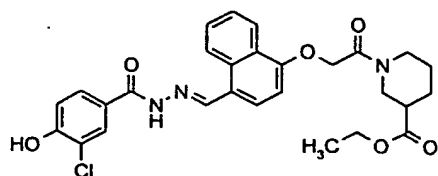
EXAMPLE 251:



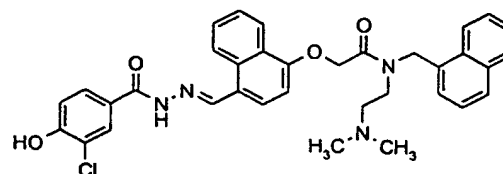
EXAMPLE 256:



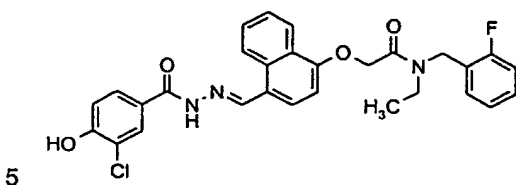
EXAMPLE 257:



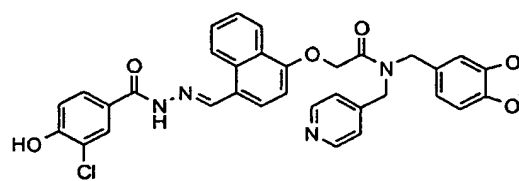
15 EXAMPLE 262:



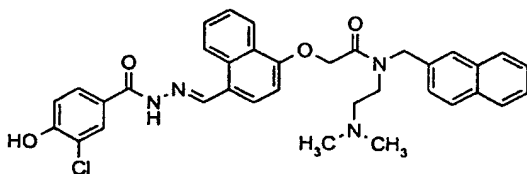
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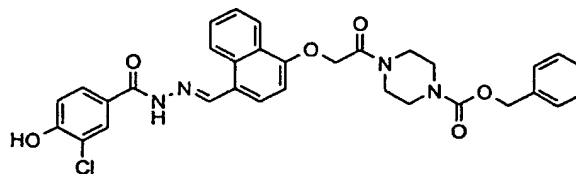
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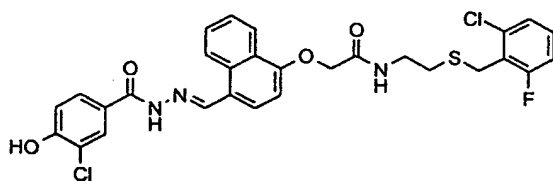
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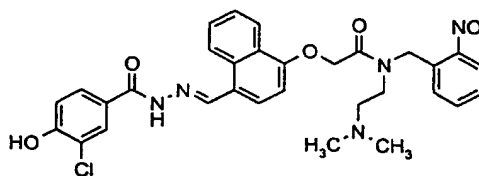
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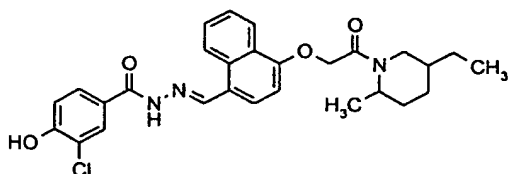
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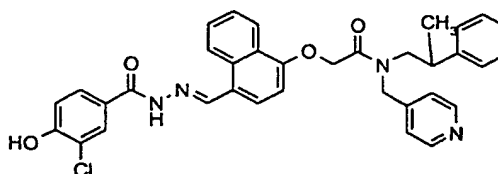
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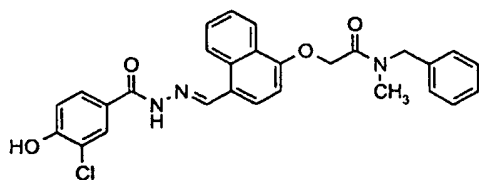
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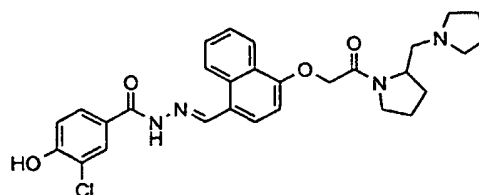
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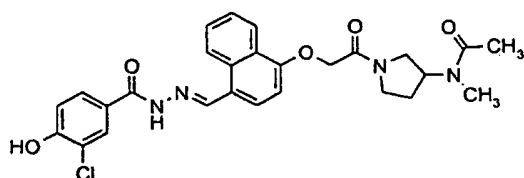
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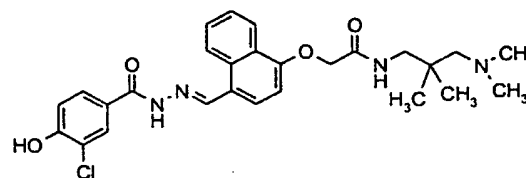
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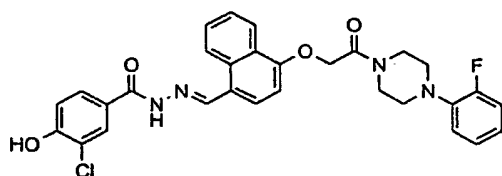
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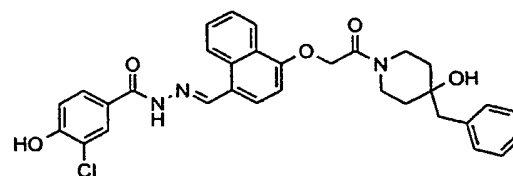
20 EXAMPLE 273:



EXAMPLE 269:

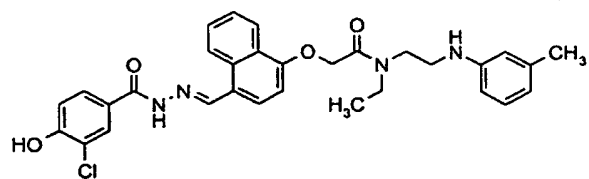


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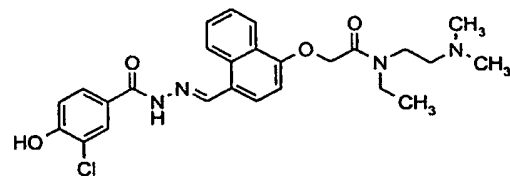
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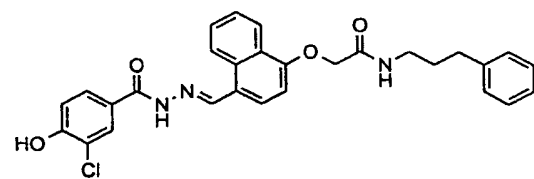


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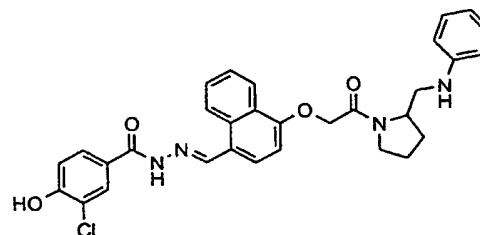


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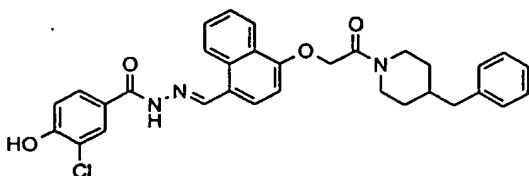


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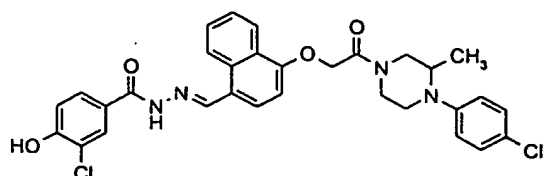
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EXAMPLE 277:

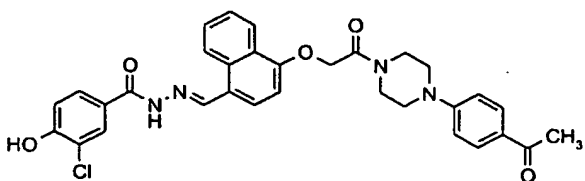


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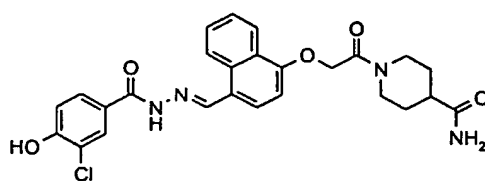


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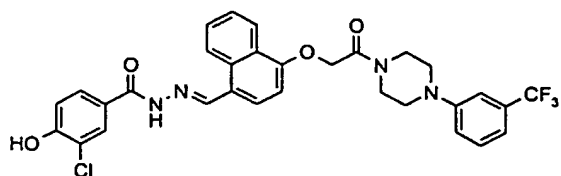
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EXAMPLE 283:

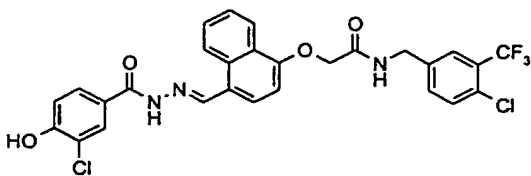


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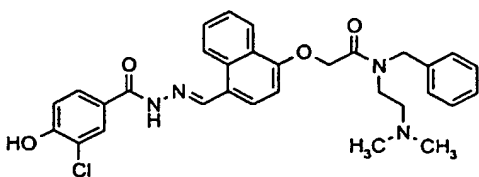
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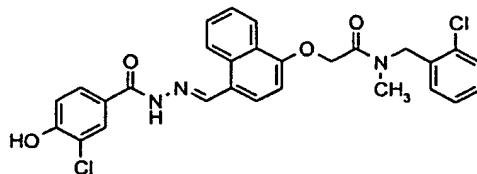


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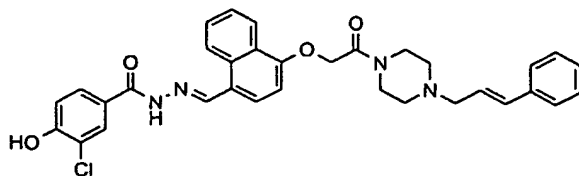
EXAMPLE 280:



EXAMPLE 285:

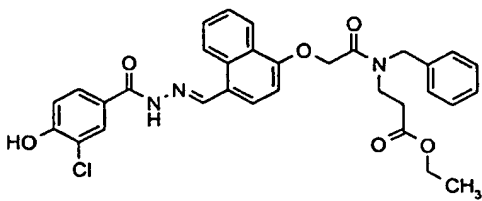


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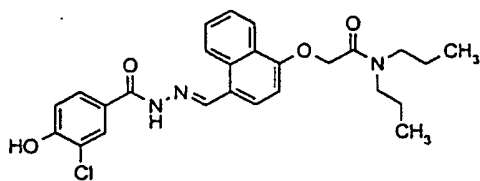


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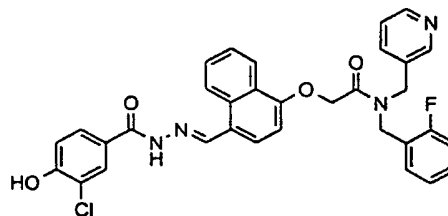
15 EXAMPLE 281:



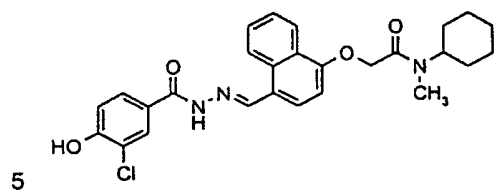
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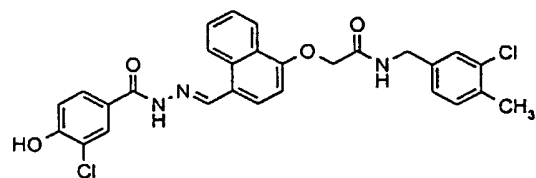
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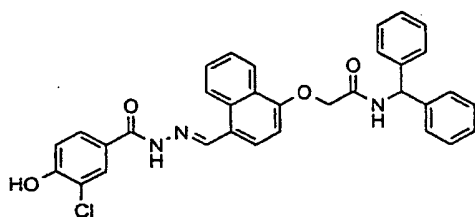
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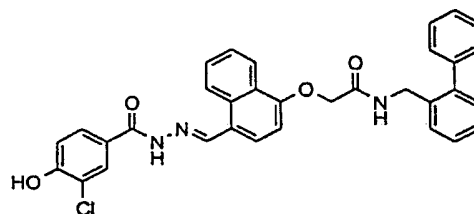
15 EXAMPLE 292:



EXAMPLE 289:

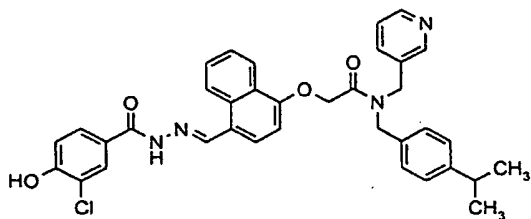


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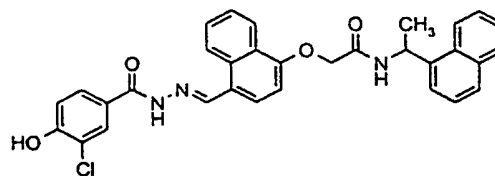


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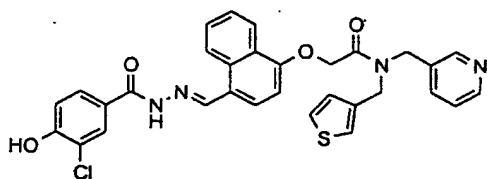
10 EXAMPLE 290:



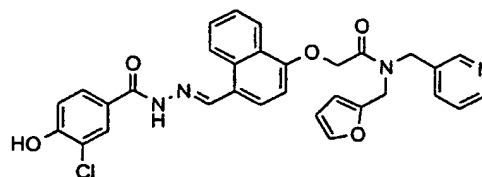
EXAMPLE 294:



EXAMPLE 295:

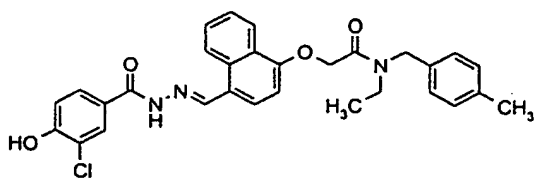


EXAMPLE 299:



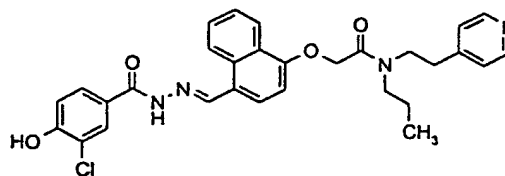
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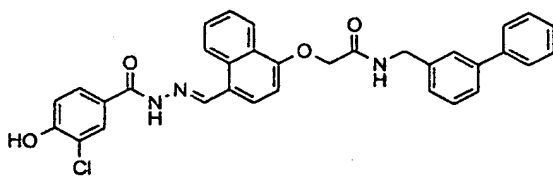


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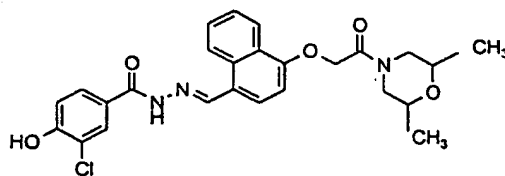
EXAMPLE 300:



EXAMPLE 297:

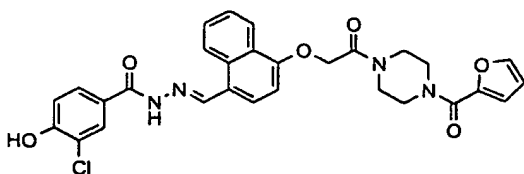


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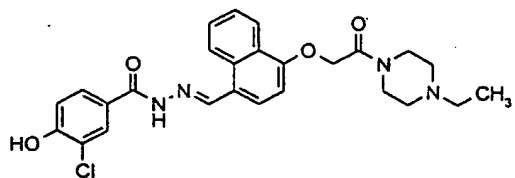


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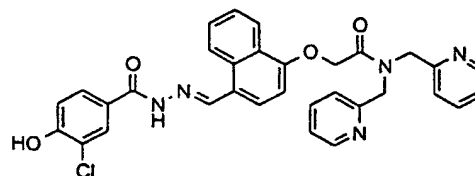
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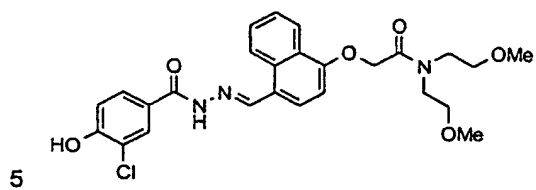
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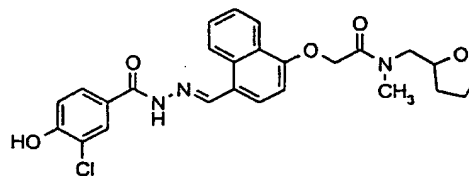
15 EXAMPLE 307:



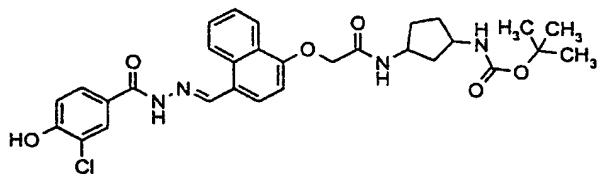
EXAMPLE 303:



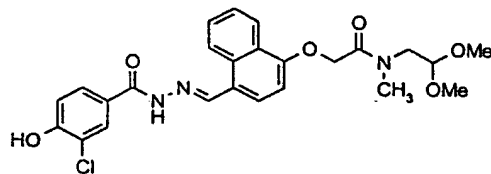
EXAMPLE 308:



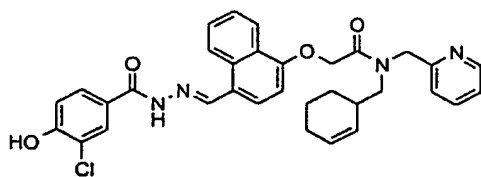
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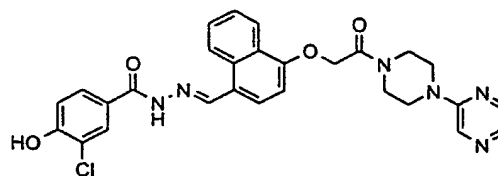
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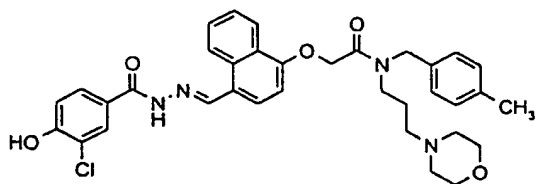
10 EXAMPLE 305:



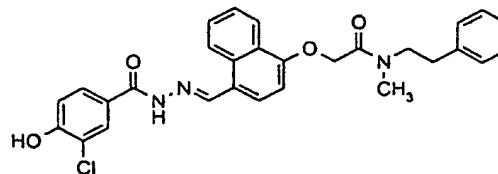
EXAMPLE 310:



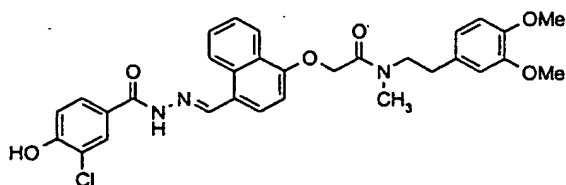
EXAMPLE 306:



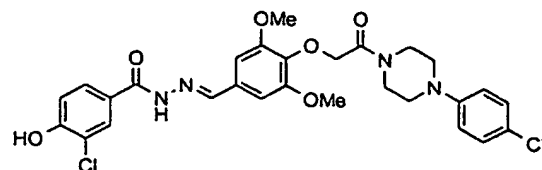
EXAMPLE 311:



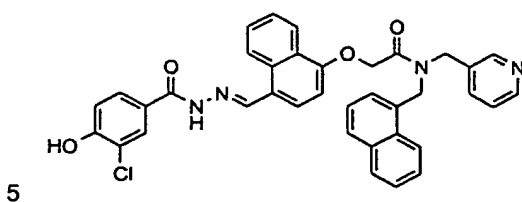
EXAMPLE 312:



15 EXAMPLE 317:

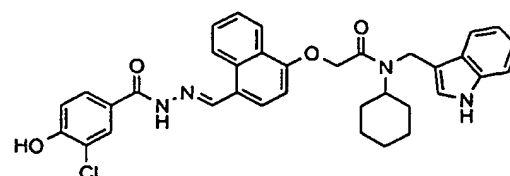


EXAMPLE 313:



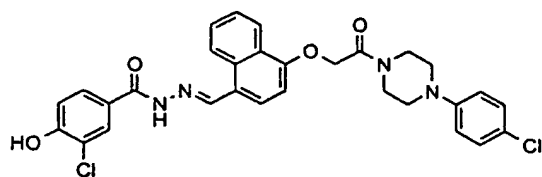
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EXAMPLE 318:

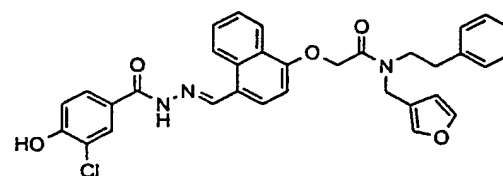


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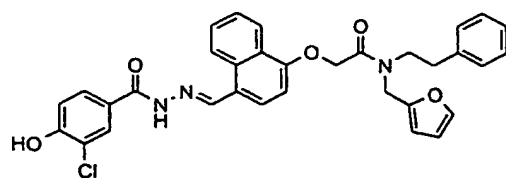
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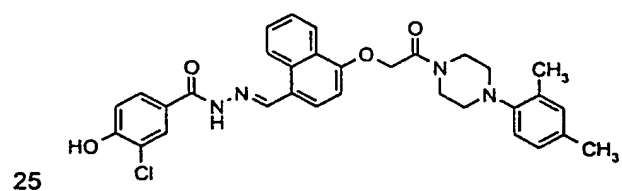
EXAMPLE 319:



10 EXAMPLE 315:

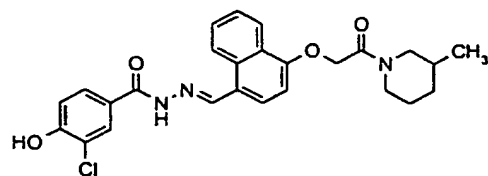


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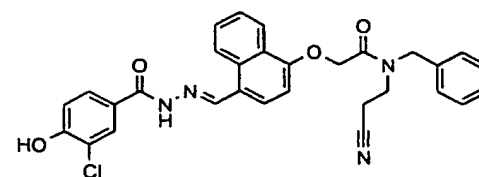


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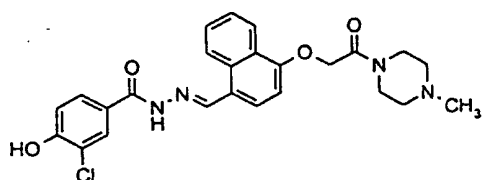
EXAMPLE 316:



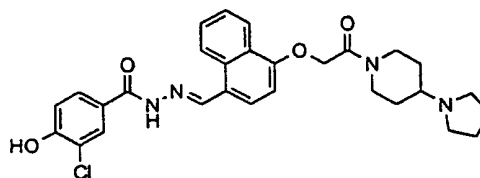
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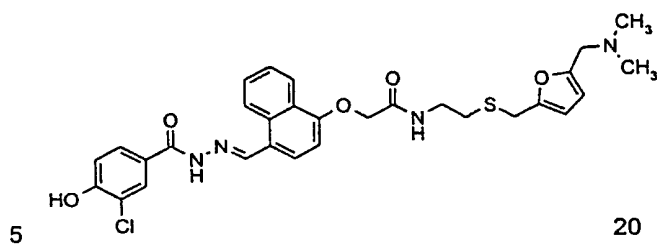
EXAMPLE 322:



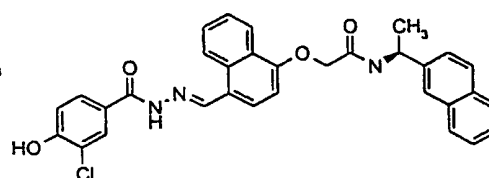
15 EXAMPLE 327:



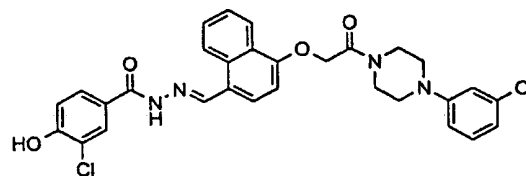
EXAMPLE 323:



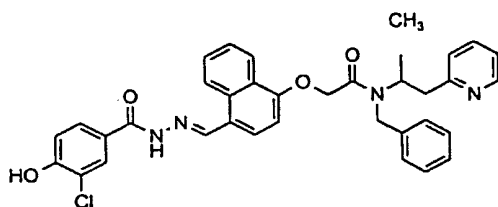
EXAMPLE 328:



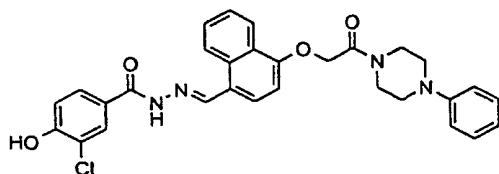
EXAMPLE 329:



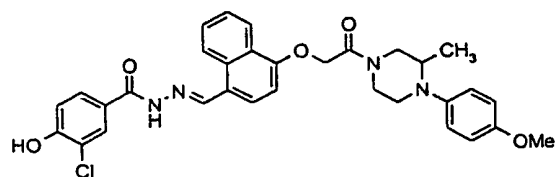
EXAMPLE 324:



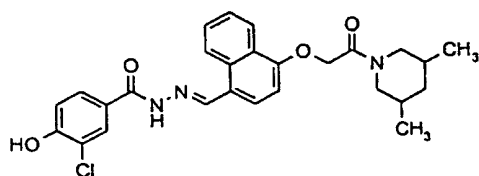
10 EXAMPLE 325:



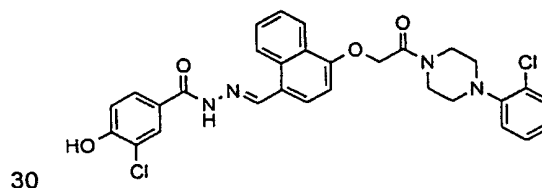
25 EXAMPLE 330:



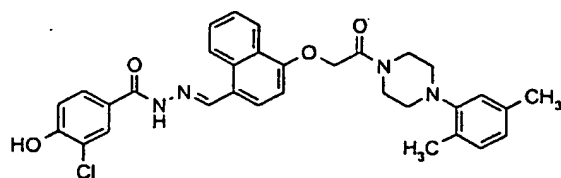
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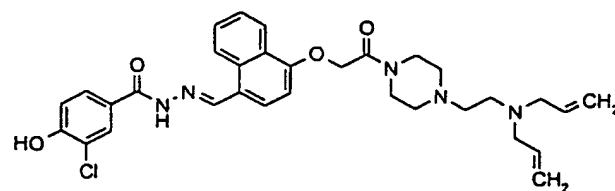
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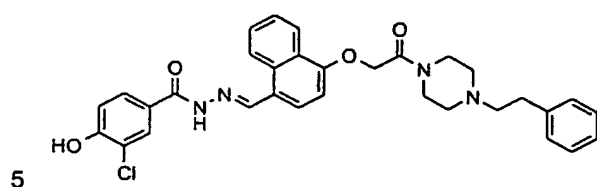
EXAMPLE 332:



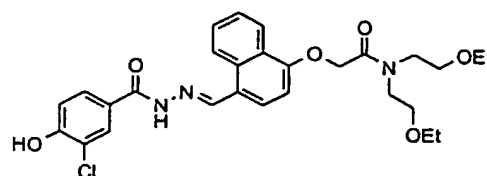
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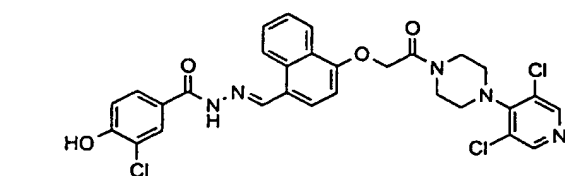
EXAMPLE 333:



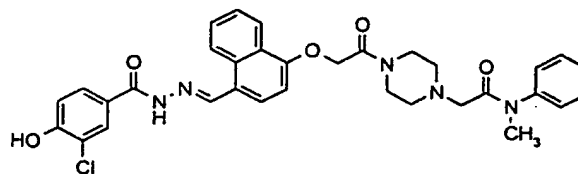
20 EXAMPLE 338:



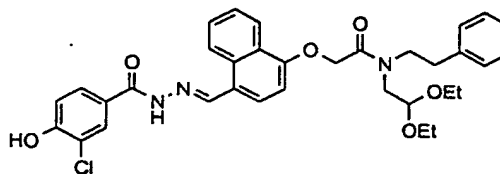
EXAMPLE 334:



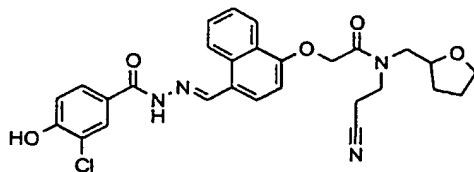
EXAMPLE 339:



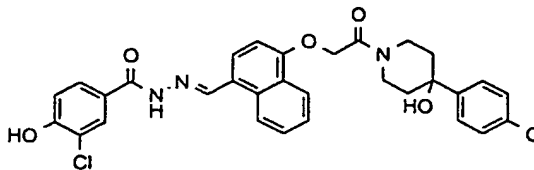
25 EXAMPLE 340:



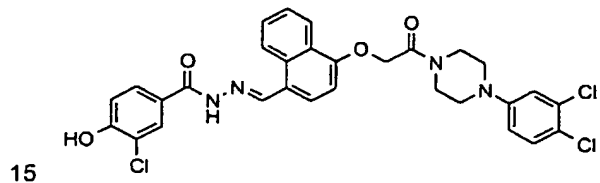
EXAMPLE 335:



EXAMPLE 341:

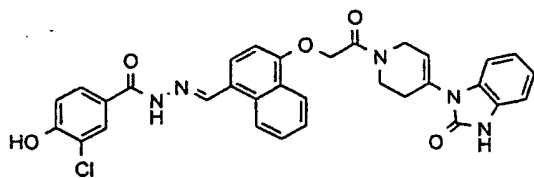


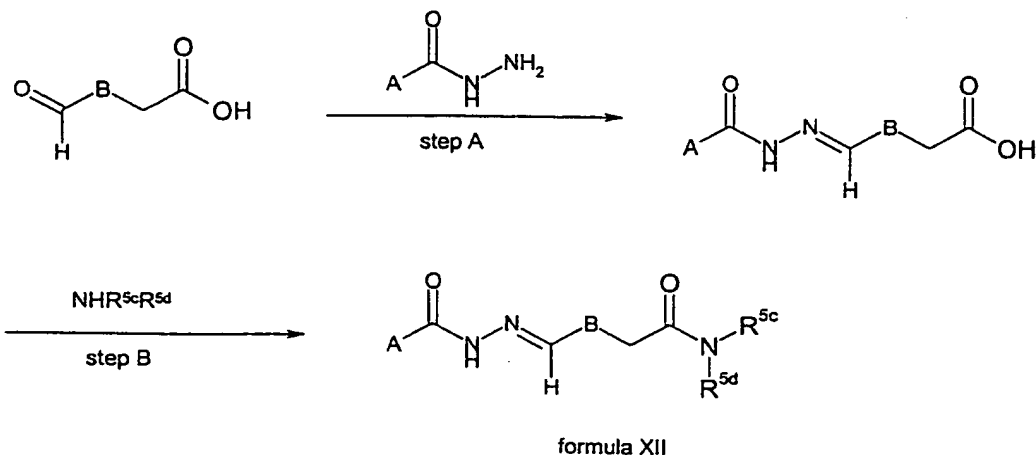
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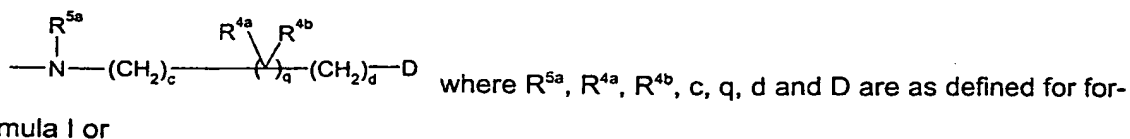
## EXAMPLE 342:

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General procedure for synthesis of compounds of the general formula XII:

- 5 A and B are as defined for formula I and  $-NR^{5c}R^{5d}$  is



-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

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Step A: The carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of  $N_2$  or Ar at temperatures between  $0^\circ\text{C}$  to  $140^\circ\text{C}$ , preferably between  $10^\circ\text{C}$  to  $80^\circ\text{C}$ . In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

20

Step B: The resulting acid is then coupled to a primary or secondary amine using one of the methods well-known to those skilled in the art. This coupling can be performed using one of the standard amide or peptide synthesis procedures such as by generating an active ester, an anhydride or an acid halide that can then react with the amine to give a compound of formula XII. Step B was also done combinatorially with a preactivated acid and a selection of amines. The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent giving a compound of formula XII.

Specific examples illustrating the preparation of compounds of the general formula XII according to the invention are provided below.

#### Preparation of 4-formyl-1-naphthylacetic acid:

This compound was prepared from the reduction of 4-cyano-1-naphthylacetic acid in the presence of 85% formic acid and Raney alloy as described in the literature. References : 1) A.A. Shulezhko and A.I. Kiprianov, J. org. Chem., (USSR) English translation, 4, 1968, p.1052. 2) Zh. Org. Khim., 4, 1968, p. 1089.

#### Preparation of 4-[3-Chloro-4-hydroxybenzoyl]-hydrazonomethyl-1-naphthylacetic acid (step A):

This compound was prepared according to the general procedure for the synthesis of alkylidene hydrazides from the condensation of 4-formyl-1-naphthylacetic acid above and 3-chloro-4-hydroxybenzoic acid hydrazide.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 4.1 (s, 2H), 7.1 (d, 1H), 7.5 (d, 1H), 7.7 (qt, 2H), 7.8 (d, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 8.1 (d, 1H), 8.8 (d, 1H), 9.1 (s, 1H), 11.0 (brd s, 1H), 11.8 (s, 1H), 12.2 (brd s, 1H); MS (APCI): 383.4, 385.2.

5 Preparation of (3-formylindolyl)acetic acid:

Ethyl (3-formylindolyl)acetate:

3-Formylindole (10.0 g, 69 mmoles) was dissolved in DMF (100 ml). Under N<sub>2</sub> was a 60% suspension of NaH in mineral oil (3.0 g) added in portions with cooling (temp < 15 °C). At < 15 °C was a solution of ethyl bromoacetate (8.4 ml) in DMF (15 ml) added drop wise over 30 minutes. The resulting mixture was stirred at room temperature for 16 hours and evaporated in vacuo. The residue was added water (300 ml) and extracted with ethyl acetate (2 x 150 ml), the combined organic extracts were washed with satd. NH<sub>4</sub>Cl, dried (MgSO<sub>4</sub>) and concentrated to afford 15.9 g ethyl (3-formylindolyl)acetate.

15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (t, 3H), 4.22 (q, 2H), 4.90 (s, 2H), 7.21 - 7.35 (m, 3H), 7.72 (s, 1H), 8.30 (d, 1H), 10.0 (s, 1H).

(3-formylindolyl)acetic acid:

20 Ethyl (3-formylindolyl)acetate (15.9 g) was dissolved in 1,4-dioxane (100 ml) and added 36% aq. NaOH (10 ml). The resulting mixture was stirred at room temperature for 4 days. Water (500 ml) was added and the mixture was washed with diethyl ether (150 ml). The aqueous phase was made acidic with 5N HCl and extracted with ethyl acetate (250 + 150 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated in vacuo to afford 10.3 g (73 % over two steps) of (3-formylindolyl)acetic acid.

25

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 4.94 (s, 2H), 7.27 - 7.36 (m, 3H), 7.98 (s, 1H), 8.25 (d, 1H), 10.0 (s, 1H), 12.5 (bs, 1H).

30 Preparation of (4-Formylindolyl)acetic acid:

4-Formylindole:

This compound was synthesized according to F. Yamada, M. Somei, *Heterocycles* 26 (1987) 1173.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.28 - 7.36 (m, 2H), 7.41 (t, J = 3.0 Hz, 1H), 7.60 - 7.70 (m, 2H), 8.62 (brd s, 1H), 10.20 (s, 1H). GC-MS (pos.): 146

Ethyl (4-formylindolyl)acetate:

This compound was synthesized according to the general procedure for N-alkylation of indoles.

10

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.13 (t, J = 6.9 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 4.86 (s, 2H), 7.22 - 7.35 (m, 3H), 7.49 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H), 10.20 (s, 1H).

(4-Formylindolyl)acetic acid:

15 This compound was synthesized according to the general procedure for saponification of esters.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 5.15 (s, 2H), 7.12 (d, J = 3.0 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 3.1 Hz, 1H), 7.71 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 10.20 (s, 1H), 12.94 (brd s, 1H).

20

Preparation of (5-formylindolyl)acetic acid:

5-Cyano-N-tosylindole:

25 In a 100 mL round-bottom flask was placed NaH (0.4 g, 60% dispersion in mineral oil, 10 mmol) and anhydrous THF (10 mL) was added. To the suspension was added a solution of 5-cyanoindole (1.0 g, 7 mmol) in anhydrous THF (10 mL) by syringe at 0°C. The mixture was stirred for 10 min, and tosyl chloride (1.6 g, 8.4 mmol) was added. After stirring at room temperature for 2 h, water (100 mL) was added. The mixture was extracted with ethyl acetate (3x50 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by column chromatography using hexane: ethyl acetate = 2:1 as eluent to yield 1.86 g (92%) of the desired product.

30

$^1\text{H}$  NMR (  $\text{CDCl}_3$  )  $\delta$  2.32 (s, 3H), 6.65 (d,  $J$  = 3.6 Hz, 1H), 7.19 (d,  $J$  = 7.9 Hz, 2H ), 7.41 (d,  $J$  = 8.6 Hz, 1H), 7.57 (d,  $J$  = 3.6 Hz, 1H), 7.63 (s, 1H), 7.75 ( d,  $J$  = 8.3 Hz, 1H), 7.99 (d,  $J$  = 8.6 Hz, 1H).

5

5-Formyl-N-tosylindole:

To a solution of 5-cyano-N-tosylindole (0.66 g, 2.2 mmol) in anhydrous THF (20 mL), was added 1M DIBAL in hexane (4 mL, 4 mmol) via syringe at 0°C. The mixture was stirred at room temperature for 16 h, poured into ice-cooled 1N hydrochloric acid (50 mL), extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated to give an oil. After a short column chromatography using hexane/ethyl acetate 2: 1 as eluent 0.62 g (95%) pure 5-formyl-N-tosylindole was obtained.

$^1\text{H}$  NMR (  $\text{CDCl}_3$  )  $\delta$  2.29 (s, 3H), 6.74 (d,  $J$  = 3.7 Hz, 1H), 7.21 (d,  $J$  = 8.3 Hz, 2H), 7.65 (d,  $J$  = 3.7 Hz, 1H), 7.77 (d,  $J$  = 8.4 Hz, 2H), 7.82 (dd,  $J$  = 1.4, 8.6 Hz, 1H), 8.02 (d,  $J$  = 1.1 Hz, 1H), 8.09 (d,  $J$  = 8.6 Hz, 1H ), 9.99 (s, 1H).

5-Formylindole:

5-formyl-N-tosylindole (0.5 g, 1.7 mmol) was dissolved in a mixture of methanol (10 mL) containing 5% aqueous KOH solution (5 mL). The mixture was refluxed for 3 h, neutralized with 1N hydrochloric acid, and extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated. The residue was purified by short column chromatography to provide 240 mg (97%) of the desired product.

$^1\text{H}$  NMR (  $\text{CDCl}_3$  )  $\delta$  6.70 (t,  $J$  = 2.1 Hz, 1H), 7.32 (t,  $J$  = 2.3 Hz, 1H), 7.49 (d,  $J$  = 8.4 Hz, 1H), 7.78 ( dd,  $J$  = 1.5, 8.6 Hz, 1H), 8.19 (s, 1H), 9.45 (b, 1H), 10.15 (s, 1H). GC-MS (pos.): 146.

Ethyl (5-formylindolyl)acetate:

This compound was synthesized according to the general procedure for N-alkylation of indoles.

30

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.27 (t, J = 6.8 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.87 (s, 2H), 6.70 (d, J = 3.4 Hz, 1H), 7.18 (d, J = 3.0 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 8.14 (s, 1H), 10.01 (s, 1H).

5 (5-Formylindolyl)acetic acid:

this compound was synthesized according to the general procedure for saponification of esters.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 5.10 (s, 2H), 6.66 (d, J = 3.0 Hz, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 8.17 (s, 1H), 9.97 (s, 1H), 12.9 (brd s, 1H).

General procedure for preparation of [(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]indolyl acetic acids:

15 These compounds were prepared according to the general procedure for the synthesis of alkylidene hydrazones by condensation of the various formylindolylacetic acids with 3-chloro-4-hydroxy benzoic acid hydrazide.

3-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]indolyl acetic acid:

20

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.81 (t, J = 6.5, 2H), 4.43 (t, J = 6.5, 2H), 7.06 (d, J = 8.5, 1H), 7.15-7.28 (m, 2H), 7.56 (d, J = 8.1, 1H), 7.75 (d, J = 8.5, 1H), 7.83 (s, 1H), 7.95 (s, 1H), 8.27 (d, J = 7.65, 1H), 8.54 (s, 1H), 10.88 (br s, 1H), 11.41 (s, 1H). LRMS calcd for C<sub>19</sub> H<sub>18</sub> Cl<sub>1</sub> N<sub>3</sub> O<sub>4</sub> (M - H) 384, found 384.0.

25

4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]indolyl acetic acid:

<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) δ 5.09 (s, 2H), 7.09 (d, J = 8.6 Hz, 1H), 7.16 - 7.25 (m, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.45 - 7.55 (m, 2H), 7.81 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 1.8 Hz, 1H), 8.68 (s, 30 1H), 10.96 (s, 1H), 11.71 (s, 1H), 12.90 (b, 1H). MS ( APCI, neg.): 370.

5-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]indolyl acetic acid:

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 5.09 (s, 2H), 6.35 (d, J = 2.9 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 3.1 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.97 (s, 1H), 8.48 (s, 1H), 10.93 (s, 1H), 11.58 (s, 1H), 12.90 (brd s, 1H). MS (APCI, neg. ): 370.

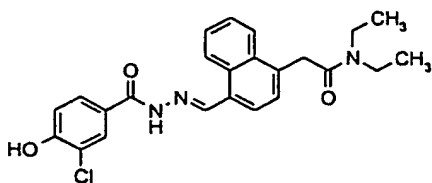
4-[3-Chloro-4-hydroxybenzoyl]-hydrazonomethyl]-1-naphthylacetamides and the various indolacetamides (step B):

General library production procedures :

To solutions of 4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]naphthylacetic acid and the various indolylacetic acids in DMSO was added carbonyldiimidazole (1.2 eq). The solution was agitated for 5 minutes and diluted with DMSO to a concentration of 50 mM. The solution was then dispensed into 88 deep well plates containing solutions of amines in DMSO (50 mM). The plates were covered and agitated for 16 hours. The products were purified by HPLC.

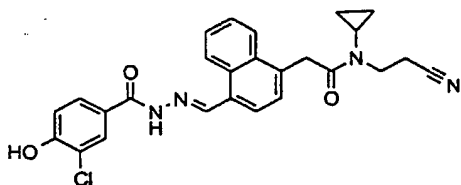
Examples of compounds of the formula XII:

EXAMPLE 343:



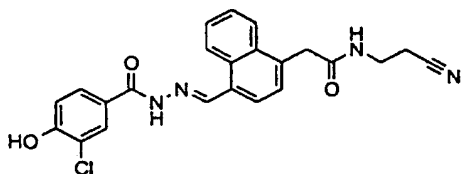
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.06 (t, 3H), 1.17 (t, 3H), 3.31 (qt, 2H), 3.50 (qt, 2H), 4.19 (s, 2H), 7.10 (d, 1H), 7.45 (d, 1H), 7.64 (quintet, 2H), 7.83 (d, 1H), 7.88 (d, 1H), 7.98 (m, 2H), 8.87 (d, 1H), 9.09 (s, 1H), 10.99 (brd s, 1H), 11.80 (brd s, 1H); ms (APCI); 438.1, 440.1.

## EXAMPLE 344:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 0.98 (d, 4H), 2.76 (t, 2H), 3.02 (quintet, 1H), 3.59 (t, 2H), 4.40 (s, 2H), 7.10 (d, 1H), 7.48 (d, 1H), 7.48 (d, 1H), 7.59 (qt, 1H), 7.67 (t, 1H), 7.81 (d, 1H), 7.89 (d, 1H), 7.97 (d, 1H), 8.02 (s, 1H), 8.84 (d, 1H), 9.09 (s, 1H), 10.99 (brd s, 1H) 11.80 (brd s, 1H); MS (APCI, neg.): 473.1, 475.1.

## EXAMPLE 345:

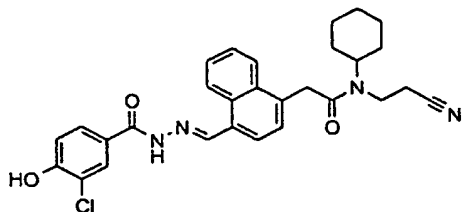


10

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.50 (2H), 2.68 (t, 2H), 4.00 (s, 2H), 7.10 (d, 1H), 7.53 (d, 1H), 7.65 (tt, 2H), 7.80 (dd, 1H), 7.90 (d, 1H), 8.02 (d, 1H), 8.14 (d, 1H), 8.62 (t, 1H), 8.84 (d, 1H), 9.09 (s, 1H), 11.0 (brd s, 1H) 11.80 (s, 1H); MS (APCI): 433.1, 435.1

15

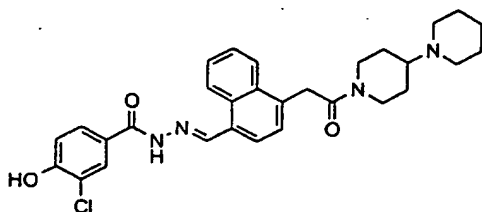
## EXAMPLE 346:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.08 (m, 4H), 1.54 (m, 6H), 2.70 (t, 2H), 3.45 (t, 2H), 3.76 (m, 1H), 4.30 (s, 2H), 7.06 (d, 1H), 7.49 (d, 1H), 7.64 (m, 2H), 7.80 (d, 1H), 7.88 (d, 1H), 8.01 (s, 1H), 8.07 (d, 1H), 8.83 (d, 1H), 9.09 (s, 1H), 10.5 (brd d, 1H), 11.78 (brd s, 1H); MS (APCI, neg.): 515.2.

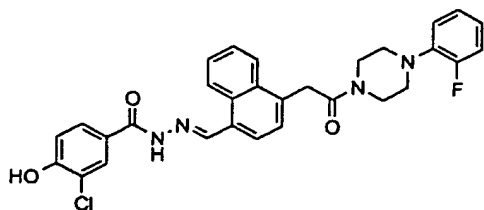
20

## EXAMPLE 347:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.26 (m, 2H), 1.37 (m, 4H), 1.67 (m, 2H), 2.43 (m, 4H), 2.62 (m, 3H),  
5 3.10 (t, 2H), 3.90 (d, 1H), 4.32 (s, 2H), 4.48 (d, 1H), 7.10 (d, 1H), 7.31 (d, 1H), 7.48 (m, 2H),  
7.81 (d, 1H), 7.88 (d, 1H), 8.03 (m, 2H), 8.85 (d, 1H), 9.08 (brd s, 1H), 11.76 (brd s, 1H); MS  
(APCI): 533.2.

## EXAMPLE 348:

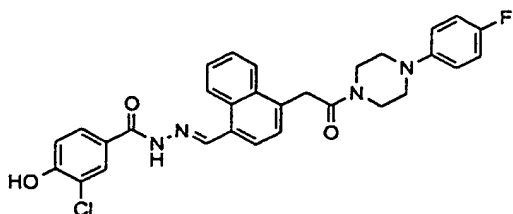


10

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.03 (m, 4H), 3.68 (t, 2H), 3.79 (t, 2H), 4.30 (s, 2H), 7.14 (m, 5H),  
7.47 (d, 1H), 7.66 (quintet, 2H), 7.82 (d, 1H), 7.88 (d, 1H), 8.02 (d, 1H), 8.07 (d, 1H), 8.87 (d,  
1H), 9.10 (s, 1H), 10.99 (s, 1H), 11.80 (s, 1H); MS (ACPI): 545.6.

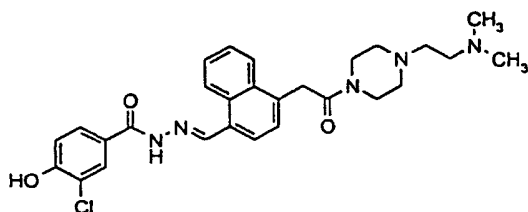
15

## EXAMPLE 349:



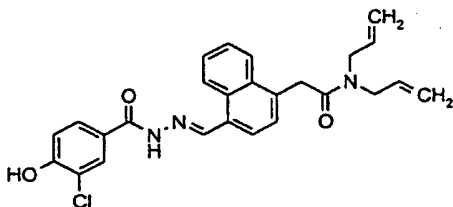
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.10 (d, 4H), 3.67 (d, 4H), 4.30 (s, 2H), 7.00 (m, 2H), 7.09 (m, 3H), 7.47 (d, 1H), 7.62 (quintet, 2H), 7.82 (d, 1H), 7.88 (d, 1H), 8.03 (s, 1H), 8.06 (d, 1H), 8.85 (d, 1H), 9.10 (s, 1H), 10.99 (s, 1H), 11.80 (s, 1H); MS (ACPI): 544.5, 545.3.

5 EXAMPLE 350:



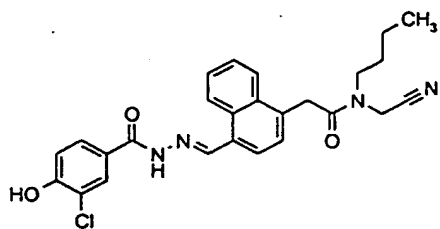
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.15 (s, 6H), 2.39 (m, 8H), 3.51 (d, 4H), 4.22 (s, 2H), 7.03 (d, 1H), 7.43 (d, 1H), 7.64 (quintet, 2H), 7.77 (d, 1H), 7.87 (d, 1H), 7.99 (s, 1H), 8.02 (d, 1H), 8.83 (d, 1H), 9.08 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 522.2.

EXAMPLE 351:



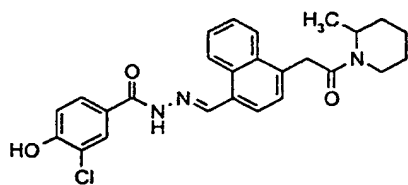
15 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 3.93 (d, 2H), 4.10 (d, 2H), 4.23 (s, 2H), 5.20 (m, 4H), 5.79 (m, 1H), 5.94 (m, 1H), 7.10 (d, 1H), 7.78 (d, 1H), 7.63 (m, 2H), 7.80 (d, 1H), 7.83 (d, 1H), 7.95 (d, 1H), 8.02 (d, 1H), 8.85 (d, 1H), 9.10 (s, 1H), 11 (brd s, 1H), 11.80 (brd s, 1H); MS (ACPI): 462.2

## EXAMPLE 352:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 0.9 (t, 3H), 1.30 (sextet, 2H), 1.54 (sextet, 2H), 3.56 (t, 2H), 4.31 (s, 2H), 4.39 (s, 2H), 7.06 (d, 1H), 7.48 (d, 1H), 7.65 (quintet, 2H), 7.79 (dd, 1H), 7.87 (d, 1H), 7.97 (d, 1H), 8.01 (d, 1H), 8.85 (d, 1H), 9.09 (s, 1H), 11.79 (s, 1H); MS (APCI): 477.01, 479.2.

## EXAMPLE 353:

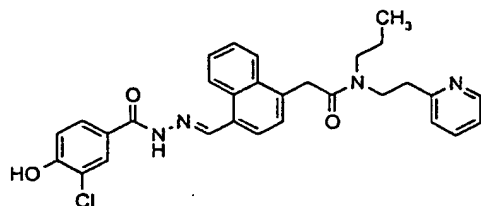


10

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.17 (m, 4H), 1.54 (m, 4H), 2.68 (m, 1H), 3.77 (d, 1H), 4.18 (s, 2H), 4.33 (m, 1H), 4.76 (brd, 1H), 7.10 (d, 1H), 7.43 (m, 1H), 7.65 (quintet, 2H), 7.81 (d, 1H), 7.88 (d, 1H), 8.02 (s, 1H), 8.04 (d, 1H), 8.84 (d, 1H), 9.09 (s, 1H), 11.79 (s, 1H); MS (APCI): 464.1, 466.2.

15

## EXAMPLE 354:

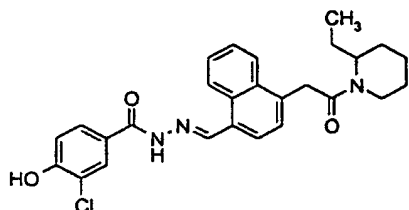


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 0.85 (qt, 3H), 1.53 (m, 2H), 3.00 (dt, 2H), 3.29 (quintet, 2H), 3.77 (dt, 2H), 4.13 (d, 2H), 7.05 (d, 1H), 7.26 (m, 2H), 7.36 (d, 1H), 7.52 (qt, 1H), 7.69 (m, 2H), 7.87

20

(m, 2H), 7.95 (d, 1H), 8.00 (s, 1H), 7.87 (dd, 1H), 8.84 (t, 1H), 9.07 (brd, 1H), 11.76 (brd s, 1H); MS (APCI): 529.2, 529.7, 531.2.

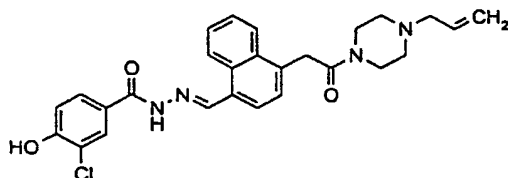
## EXAMPLE 355:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 0.85 (qt, 3H), 1.33 (m, 1H), 1.65 (m, 7H), 2.60 (t, 0.5H), 3.10 (t, 0.5H) 3.80 (m, 1H), 4.21 (s, 2H), 4.24 (m, 1H), 7.11 (d, 1H), 7.45 (t, 1H), 7.65 (m, 2H), 7.75 (d, 1H), 7.89 (d, 1H), 8.01 (d, 1H), 8.05 (d, 1H), 8.83 (d, 1H), 9.09 (s, 1H), 11.80 (s, 1H); MS (APCI): 478.4, 480.3.

10

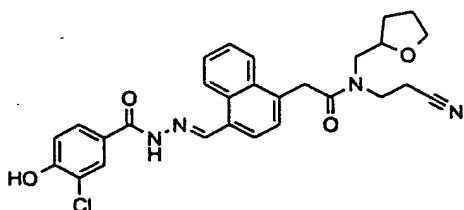
## EXAMPLE 356:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.36 (m, 4H), 2.97 (d, 2H), 3.50 (m, 2H), 3.60 (m, 2H), 4.23 (s, 2H), 5.17 (t, 2H), 5.86 (m, 1H), 7.08 (d, 1H), 7.43 (d, 1H), 7.64 (quintet, 2H), 7.79 (dd, 1H), 7.87 (d, 1H), 8.01 (s, 1H), 8.04 (d, 1H), 8.83 (d, 1H), 9.09 (d, 1H), 11.79 (brd s, 1H); MS (APCI): 491.2, 493.2.

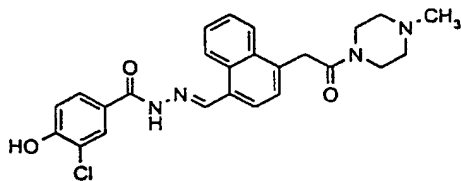
20

## EXAMPLE 357:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.50 (m, 1H), 1.90 (m, 2H), 1.95 (m, 1H), 2.72 (t, 1H), 2.95 (t, 1H),  
 5 3.30 (m, 1H), 3.55 (m, 1H), 3.65 (t, 2H), 3.75 (m, 1H), 3.92 (t, 1H), 4.12 (t, 1H) 4.35 (d, 2H),  
 7.11 (d, 1H), 7.48 (m, 1H), 7.65 (t, 1H), 7.68 (t, 1H), 7.8 (dd, 1H), 7.87 (d, 1H), 8.00 (d, 1H),  
 8.03 (d, 1H), 8.83 (d, 1H), 9.10 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 519.5, 521.2, 522.2.

## EXAMPLE 358:

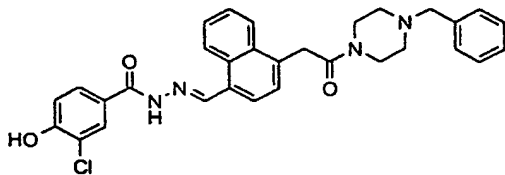


10

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.19 (s, 3H), 2.30 (m, 4 H), 3.50 (T, 2H), 3.58 (T, 2H), 4.22 (S, 2H),  
 7.03 (D, 1H), 7.43 (D, 1H), 7.64 (quint, 2H) 7.77 (dd, 1H), 7.87 (d, 1H), 7.99 (d, 1H), 8.04 (s,  
 1H), 8.83 (d, 1H), 9.09 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 465.2, 467.3.

15

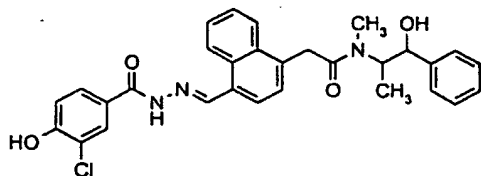
## EXAMPLE 359:



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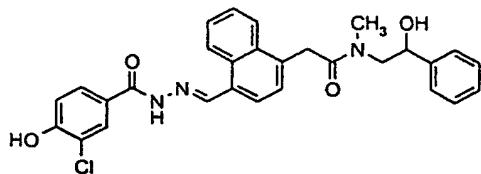
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.38 (m, 4H), 3.51 (s, 4H), 3.61 (t, 2H), 4.22 (s, 2H), 7.08 (d, 1H),  
 7.31 (m, 5H), 7.43 (d, 1H), 7.61 (quintet, 2H), 7.82 (dd, 1H), 7.88 (d, 1H), 8.00 (s, 1H), 8.02  
 (d, 1H), 8.85 (d, 1H), 9.10 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 541.4, 543.1.

## EXAMPLE 360:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.33 (dd, 3H), 2.76 (s, 1.5H), 2.96 (s, 1.5H), 3.61 (d, 1H), 4.14  
 5 (quintet, 1H), 4.65 (m, 2H), 7.10 (m, 2H), 7.33 (s, 3H), 7.42 (m, 3H), 7.54 (m, 2H), 8.02 (t, 1H), 8.80 (m, 1H), 9.07 (brd, 1H), 11.80 (brd s, 1H); MS (APCI): 530.2, 532.2.

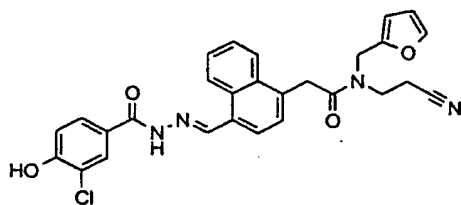
## EXAMPLE 361:



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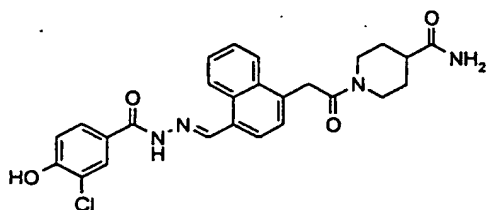
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ[2.94 (s, 1.5H) + 3.10 (s, 1.5H), 3H], 3.54 (m, 2H), 4.00 (d, 1H), 4.28  
 (d, 1H), 4.81 (t, 1H), 4.96 (t, 1H), 7.09 (d, 1H), 7.35 (m, 3H), 7.43 (m, 3H), 7.61 (m, 2H), 7.83  
 (m, 3H), 8.04 (s, 1H), 8.85 (t, 1H), 9.11 (d, 1H), 11.80 (brd s, 1H); MS (APCI): 516.3, 518.2.

## 15 EXAMPLE 362:



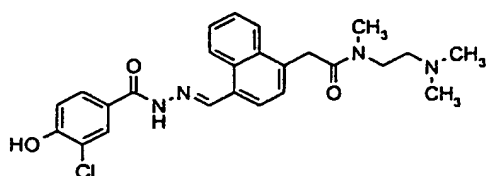
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.75 (t, 1H), 2.95 (t, 1H), 3.59 (t, 1H), 3.80 (t, 1H), 4.38 (brd s, 3H),  
 4.61 (s, 1H), 4.84 (s, 1H), 6.40 (d, 1H), 6.53 (d, 1H), 7.05 (d, 1H), 7.45 (t, 1H), 7.58 (m, 3H),  
 20 7.81 (m, 3H), 8.00 (brd, 2H), 8.83 (d, 1H), 9.10 (s, 1H), 11.78 (brd s, 1H); MS (APCI, neg.):  
 513.3, 514.2.

## EXAMPLE 363:



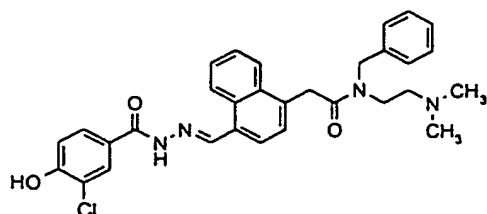
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.50 (m, 2H), 1.68, (d, 2H), 2.28 (t, 1H), 2.59 (t, 1H), 3.05 (t, 1H),  
5 3.96 (d, 1H), 4.16 (s, 2H), 4.32 (d, 1H), 6.74 (brd s, 1H), 6.95 (d, 1H), 7.22 (brd s, 1H), 7.36  
(d, 1H), 7.57 (quintet, 2H), 7.71 (dd, 1H), 7.79 (d, 1H), 7.92 (dd, 1H), 7.96 (d, 1H), 8.76 (d,  
1H), 9.01 (s, 1H), 11.80 (brd s, 1H); MS (ACPI): 493.1, 495.2.

## 10 EXAMPLE 364:



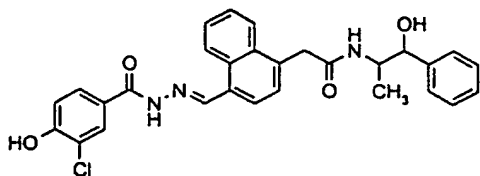
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.10 (s, 3H), 2.15 (s, 3H), 2.29 (t, 1H), 2.40 (t, 1H), 2.80 (s, 1H), 3.05  
(s, 2H), 3.36 (t, 1H), 3.46 (t, 1H), 4.16 (d, 2H), 7.01 (d, 1H), 7.38 (t, 1H), 7.56 (m, 2H), 7.72  
15 (dd, 1H), 7.79 (d, 1H), 7.94 (m, 2H), 8.77 (d, 1H), 9.02 (s, 1H), 11.71 (brd s, 1H); MS (ACPI):  
467.3, 469.1.

## EXAMPLE 365:

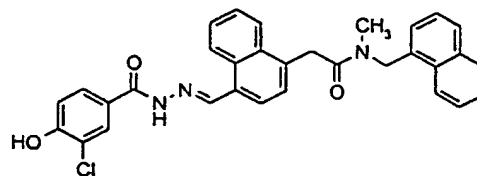


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.11 (s, 3H), 2.14 (s, 3H), 2.33 (t, 1H), 2.39 (t, 1H), 3.37 (t, 1H), 3.46 (t, 1H), 4.14 (s, 1H), 4.32 (s, 1H), 4.55 (s, 1H), 4.74 (s, 1H), 7.05 (d, 1H), 7.23 (d, 1H), 7.29 (m, 3H), 7.38 (t, 1H), 7.43 (d, 1H), 7.57 (m, 2H), 7.81 (m, 2H), 7.97 (s, 1H), 8.06 (d, 1H), 8.79 (t, 1H), 9.05 (s, 1H), 11.75 (brd s, 1H); MS (APCI): 543.2, 545.2.

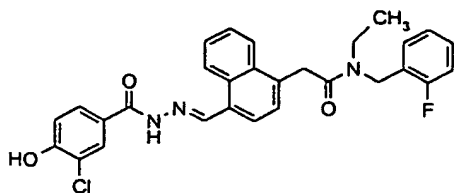
EXAMPLE 366:



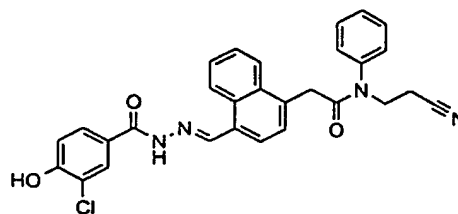
EXAMPLE 371:



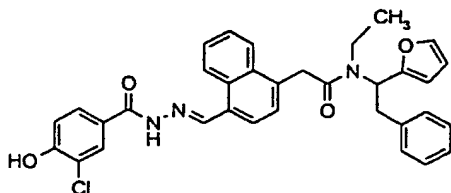
EXAMPLE 367:



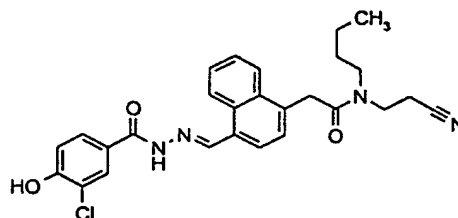
EXAMPLE 372:



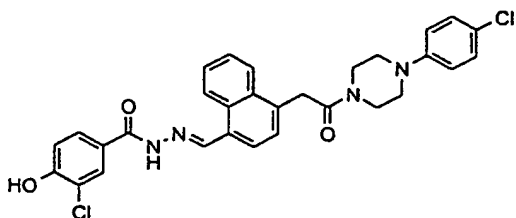
5 EXAMPLE 368:



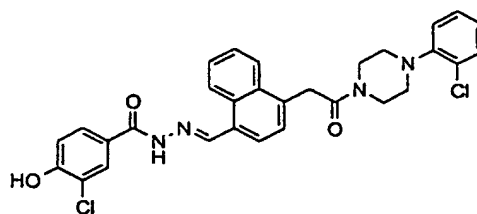
15 EXAMPLE 373:



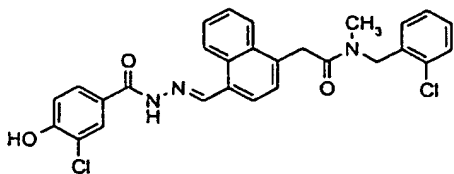
EXAMPLE 369:



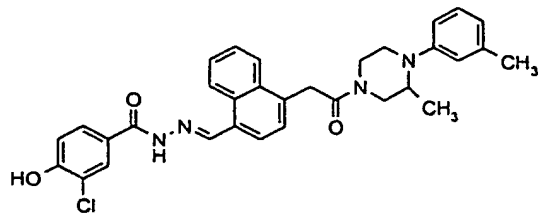
EXAMPLE 374:



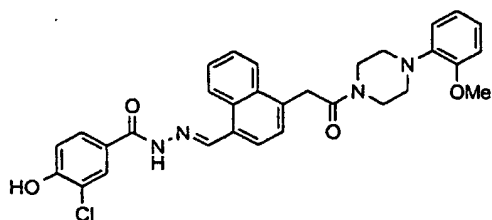
EXAMPLE 370:



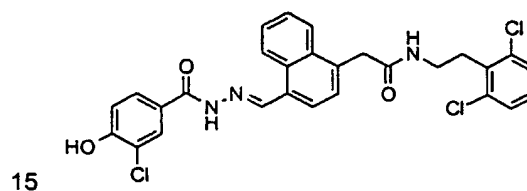
EXAMPLE 375:



EXAMPLE 376:

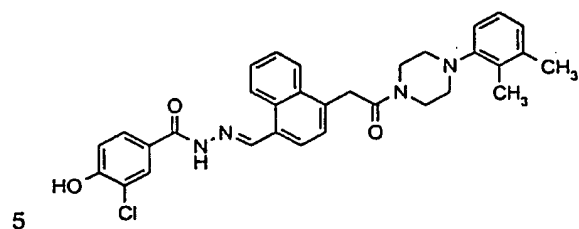


EXAMPLE 381:



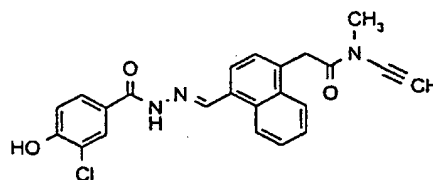
15

EXAMPLE 377:

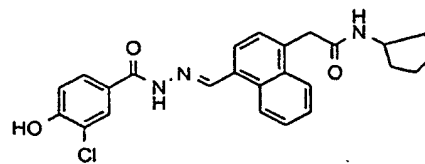


5

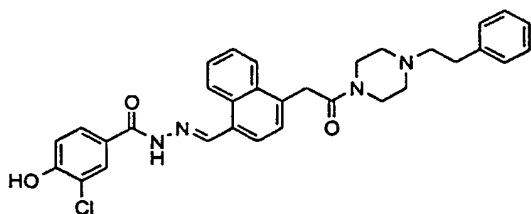
EXAMPLE 382:



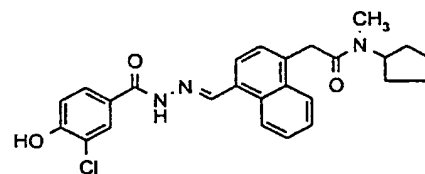
20 EXAMPLE 383:



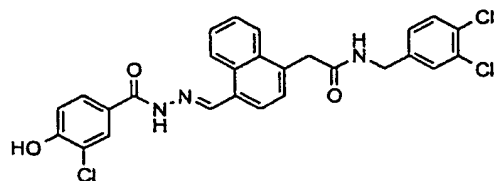
EXAMPLE 378:



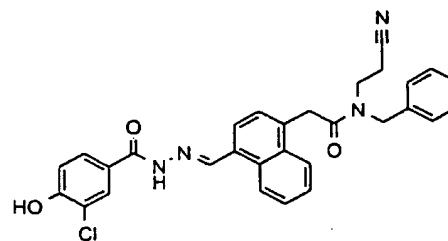
EXAMPLE 384:



10 EXAMPLE 379:

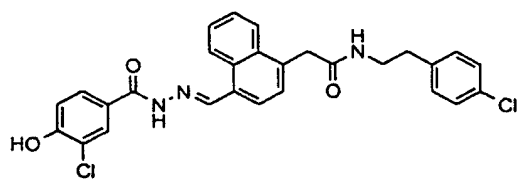


EXAMPLE 385:

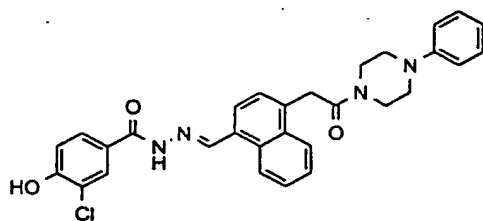


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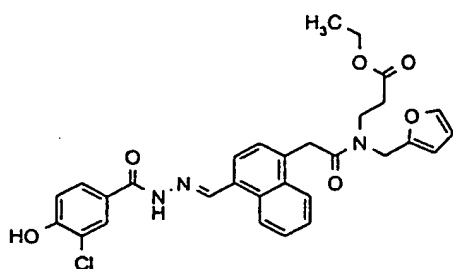
EXAMPLE 380:



EXAMPLE 386:

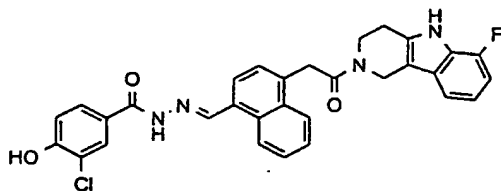


EXAMPLE 387:

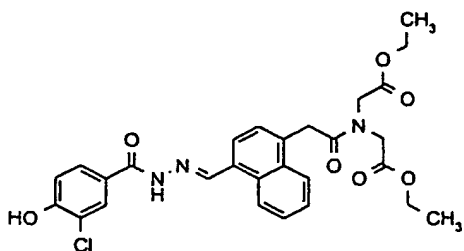


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EXAMPLE 388:

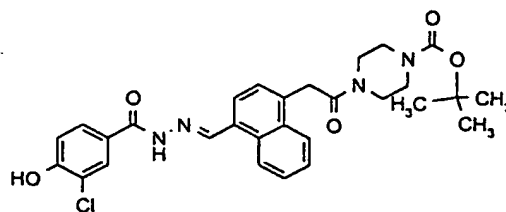


EXAMPLE 389:

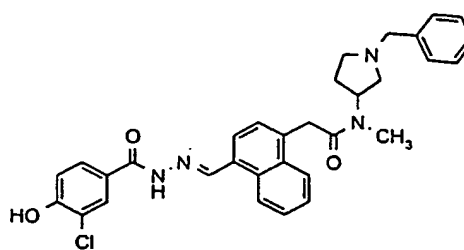


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EXAMPLE 390:

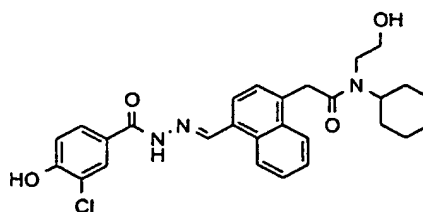


EXAMPLE 391:

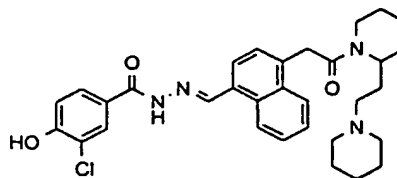


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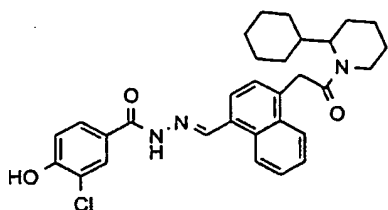
EXAMPLE 392:



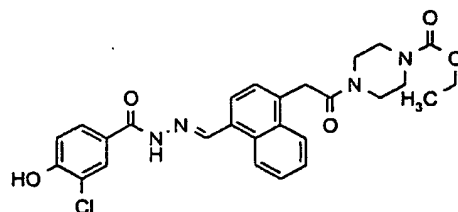
20 EXAMPLE 393:



EXAMPLE 394:

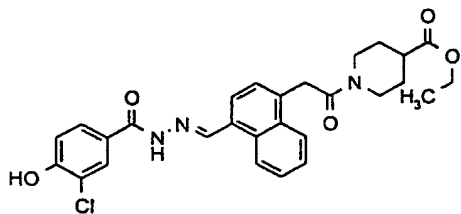


EXAMPLE 398:



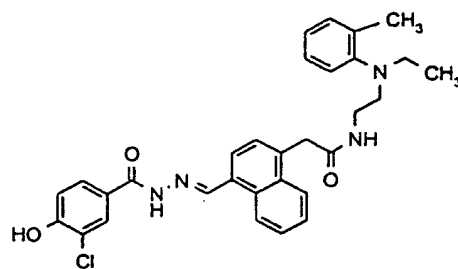
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EXAMPLE 395:

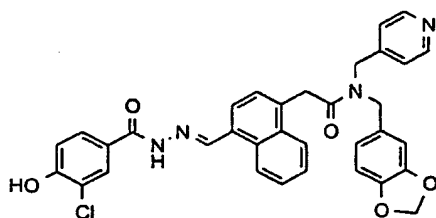


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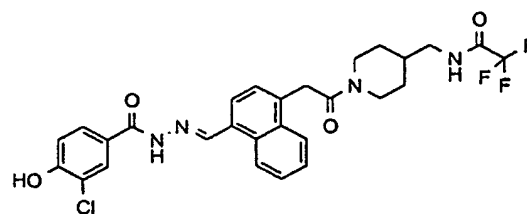
EXAMPLE 399:



EXAMPLE 396:

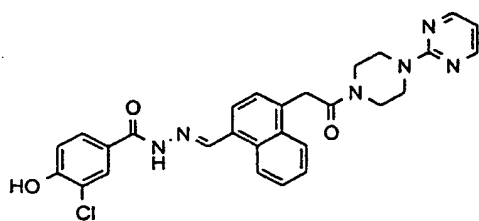


EXAMPLE 400:

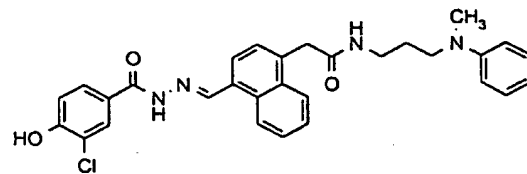


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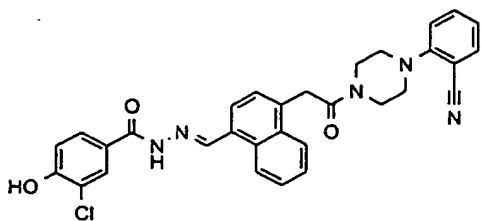
10 EXAMPLE 397:



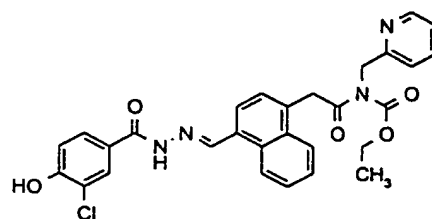
EXAMPLE 401:



EXAMPLE 402:

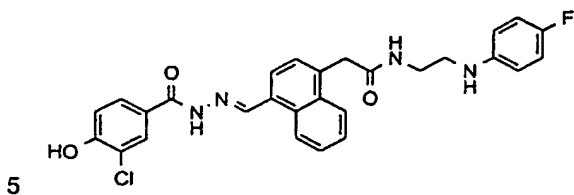


EXAMPLE 406:



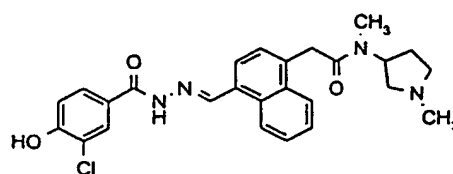
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EXAMPLE 403:

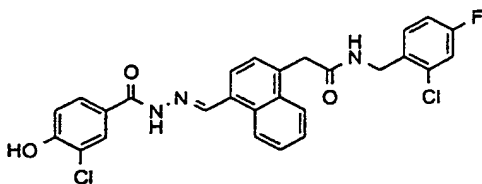


5

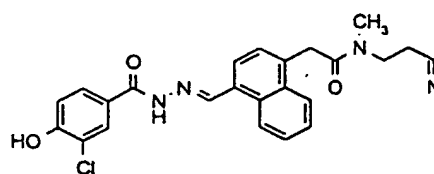
EXAMPLE 407:



EXAMPLE 404:

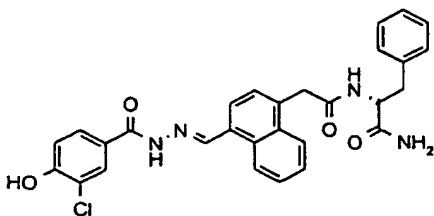


EXAMPLE 408:

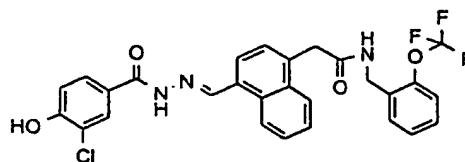


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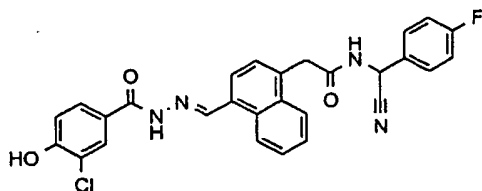
10 EXAMPLE 405:



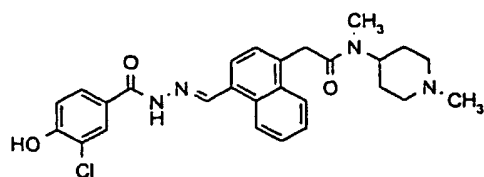
EXAMPLE 409:



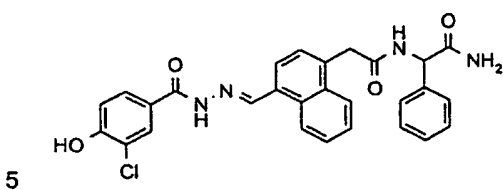
EXAMPLE 410:



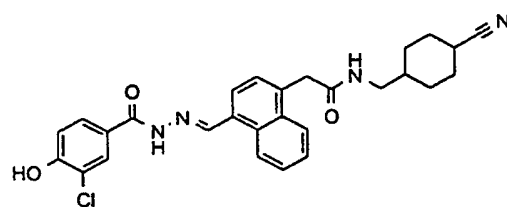
15 EXAMPLE 415:



EXAMPLE 411:

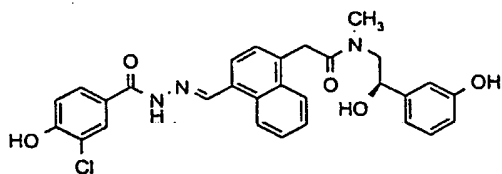


EXAMPLE 416:

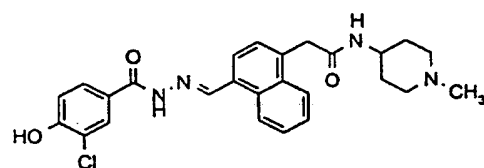


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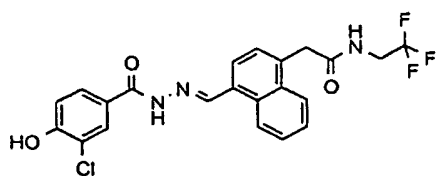
EXAMPLE 412:



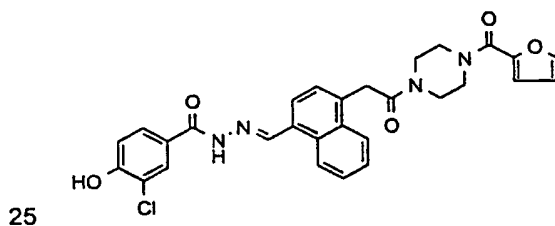
EXAMPLE 417:



10 EXAMPLE 413:

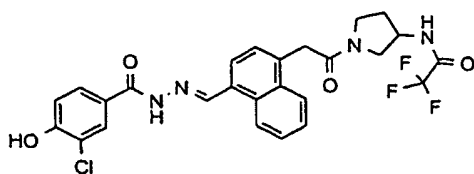


EXAMPLE 418:

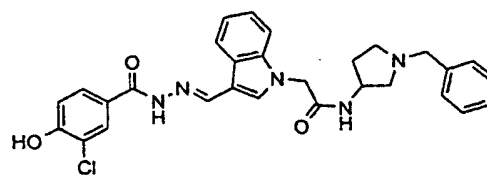


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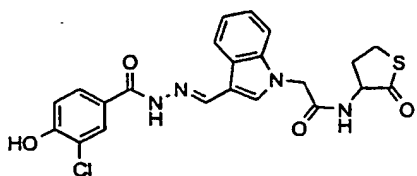
EXAMPLE 414:



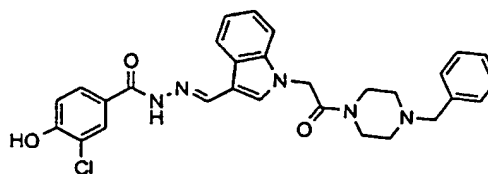
EXAMPLE 419:



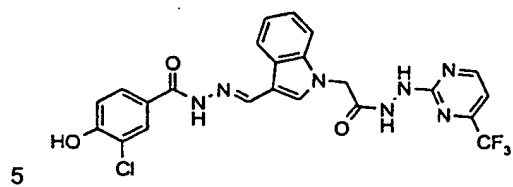
EXAMPLE 420:



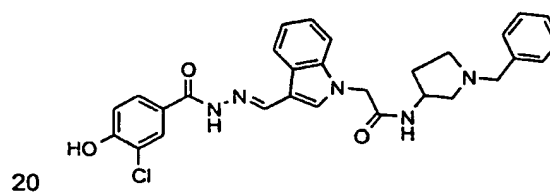
EXAMPLE 425:



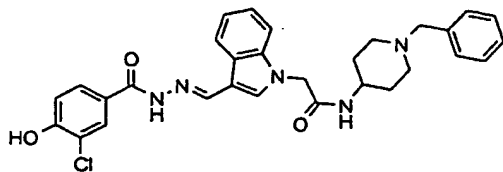
EXAMPLE 421:



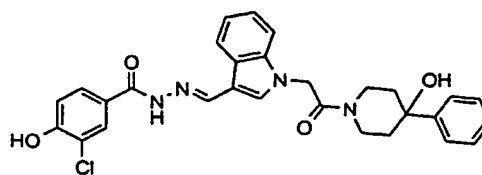
EXAMPLE 426:



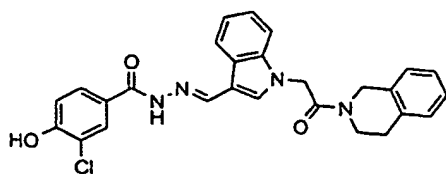
EXAMPLE 422:



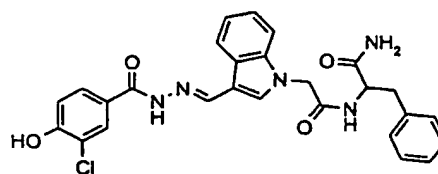
EXAMPLE 427:



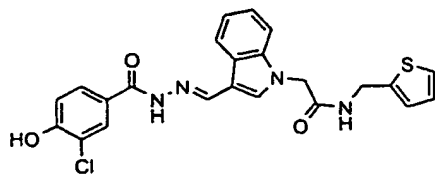
10 EXAMPLE 423:



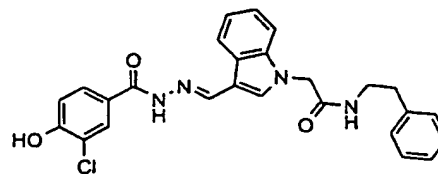
25 EXAMPLE 428:



EXAMPLE 424:

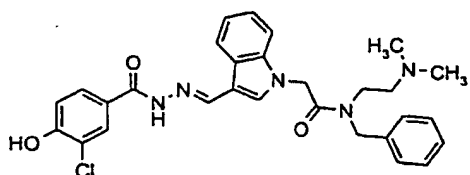


EXAMPLE 429:



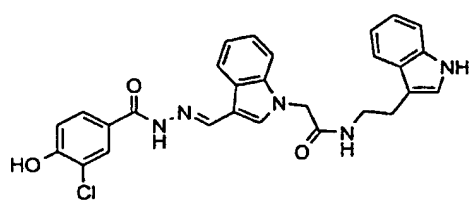
## EXAMPLE 430:

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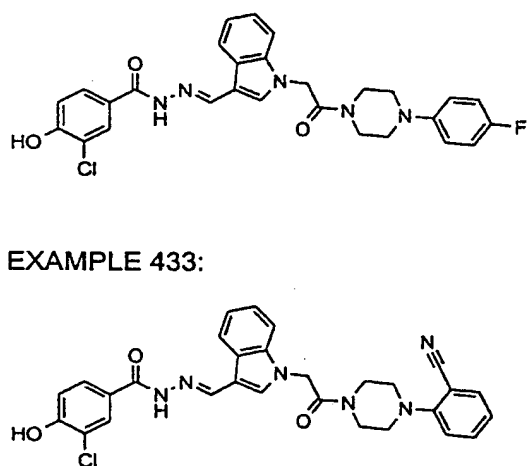
## EXAMPLE 431:

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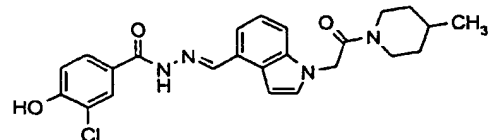


## EXAMPLE 432:

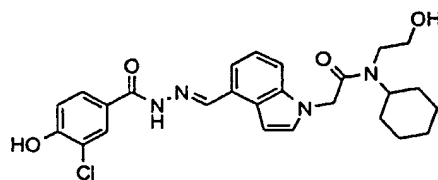
15



## EXAMPLE 434:

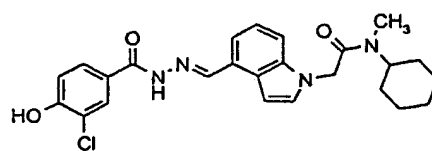


## 20 EXAMPLE 435:

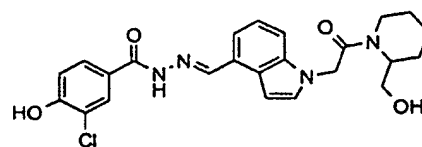


## EXAMPLE 436:

25

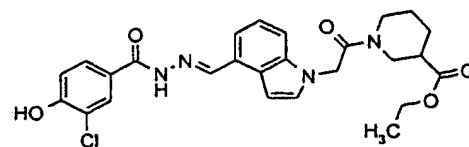


## EXAMPLE 437:

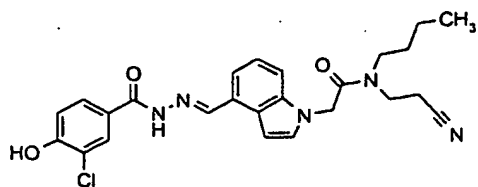


## EXAMPLE 438:

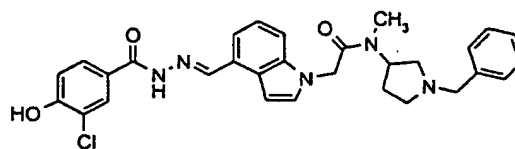
30



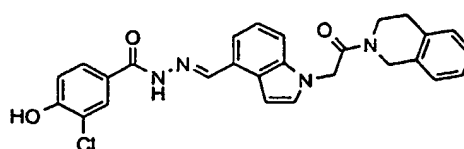
EXAMPLE 439:



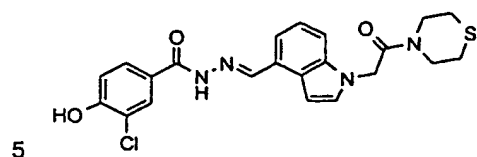
EXAMPLE 444:



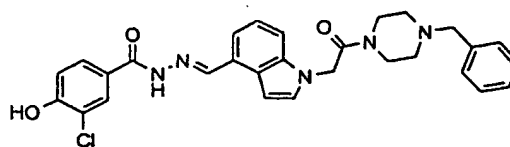
EXAMPLE 445:



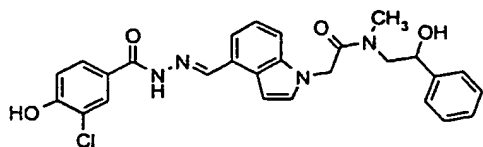
EXAMPLE 440:



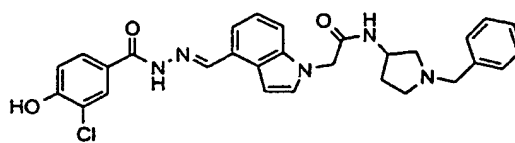
EXAMPLE 446:



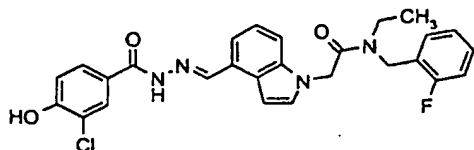
EXAMPLE 441:



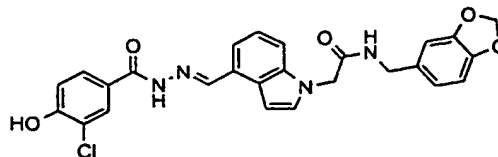
EXAMPLE 447:



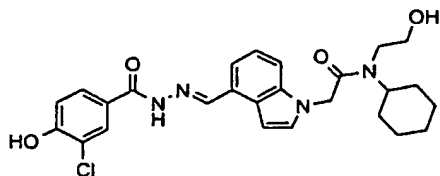
EXAMPLE 442:



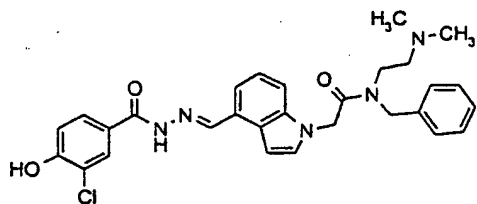
EXAMPLE 448:



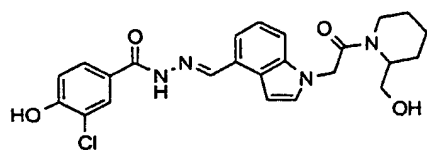
EXAMPLE 443:



EXAMPLE 449:

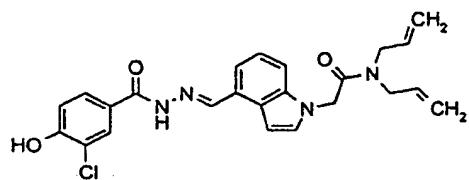


EXAMPLE 450:

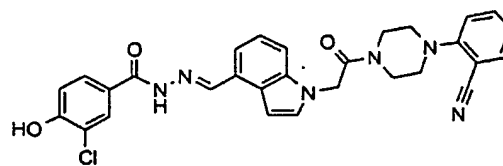


5

EXAMPLE 451:

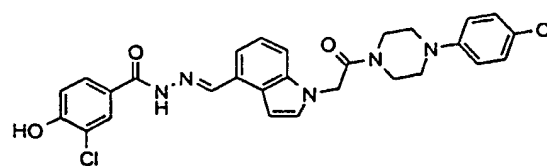


EXAMPLE 452:

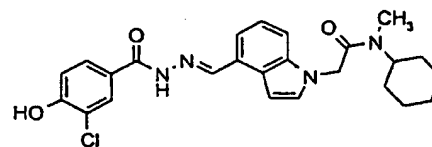


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EXAMPLE 453:

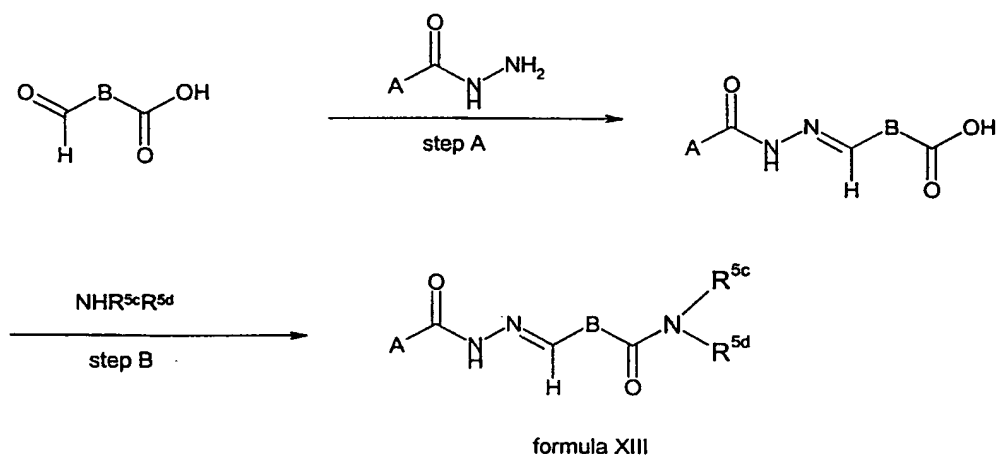


EXAMPLE 454:

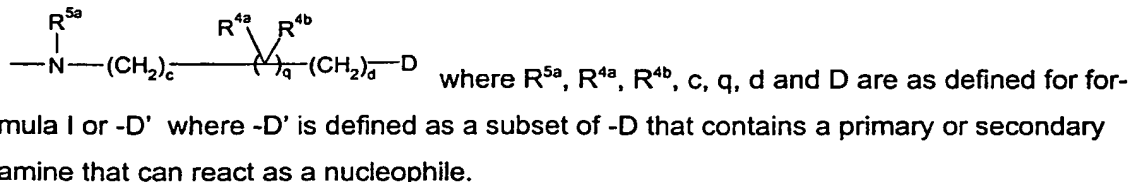


15

General procedure for synthesis of compounds of the general formula XIII:



- 5 A and B are as defined for formula I and  $\text{-NR}^{5c}\text{R}^{5d}$  is

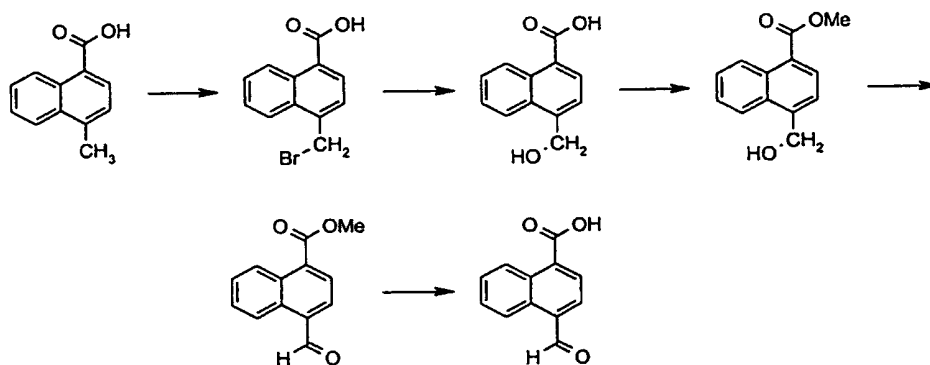


- 10 Step A: The carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of  $\text{N}_2$  or Ar at temperatures between  $0^\circ\text{C}$  to  $140^\circ\text{C}$ , preferably between  $10^\circ\text{C}$  to  $80^\circ\text{C}$ . In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product
- 15 can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.
- 20

- Step B: The resulting acid is then coupled to a primary or secondary amine using one of the methods well-known to those skilled in the art. This coupling can be performed using one of the standard amide or peptide synthesis procedures such as by generating an active ester, an anhydride or an acid halide that can then react with the amine to give a compound of formula XIII.
- 5 The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol,
- 10 toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent giving a compound of formula XIII.
- 15 Specific examples illustrating the preparation of compounds of the general formula XIII according to the invention are provided below.

Preparation of 4-formylnaphthoic acid is depicted below:

20



4-Bromomethylnaphthoic acid:

- 25 A mixture of 4-methylnaphthoic acid (10 g, 54 mmol), N-bromosuccinimide (10 g, 56 mmol) and AIBN (100 mg) in  $\text{CCl}_4$  (250 mL) was refluxed for 3 hr. The reaction mixture was con-

centrated and dissolved in ethyl acetate. The organic layer was washed with water, brine and dried over  $\text{MgSO}_4$ . Evaporation of the solvent gave the desired product (16 g, 80%).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  5.24 (s, 2H), 7.73 (m, 3H), 8.03 (d, 1H), 8.28 (d, 1H), 8.86 (d, 1H),  
5 13.29 (brd s, 1H).

4-Hydroxymethylnaphthoic acid:

4-Bromomethylnaphthoic acid (16 g, 60 mmol) in an aqueous solution of  $\text{K}_2\text{CO}_3$  (10%, 100  
10 mL) was stirred at 70 °C for 30 minutes. The reaction mixture was cooled and made acidic with conc. HCl. The resulting precipitate was filtered and dried to give the desired product as a yellow solid in quantitative yield.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ) ;  $\delta$  5.01 (s, 2H), 5.96 (s, 1H), 7.70 (m, 3H), 8.10 (m, 2H), 8.90 (d, 1H).  
15

Methyl 4-hydroxymethylnaphthoate:

A mixture of 4-hydroxymethylnaphthoic acid (10 g, 50 mmol), methanol (300 mL), and conc.  $\text{H}_2\text{SO}_4$  (2 mL) was refluxed overnight. The insolubles were filtered off and the filtrate was concentrated. The residue was taken up in ethyl acetate and washed with aqueous  $\text{NaHCO}_3$   
20 (2x), brine, dried over  $\text{MgSO}_4$ , and concentrated to give a yellow oil. Silica gel column chromatography using ethyl acetate/hexane (1/3) gave the desired product as a yellow oil (3.3 g, 35%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.05 (t, 1H), 4.01 (s, 3H), 5.22 (s, 2H), 7.66 (m, 3H), 8.09 (d, 1H), 8.16  
25 (d, 1H), 8.96 (d, 1H).

Methyl 4-formylnaphthoate:

To a solution of methyl 4-hydroxymethylnaphthoate above (3.3 g, 15.3 mmol) in dichloromethane (20 mL) was added  $\text{MnO}_2$  (6.6 g, 76 mmol). After stirring the dark mixture for 16  
30 hours, the insolubles were filtered through a bed of Celite. Evaporation of the solvent gave the desired product as a white solid in quantitative yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.06 (s, 3H), 7.75 (m, 2H), 8.03 (d, 1H), 8.20 (d, 1H), 8.80 (d, 1H), 9.27 (d, 1H), 10.50 (s, 1H).

4-Formylnaphthoic acid:

- 5 A mixture of the methyl 4-formylnaphthoate above (2.3 g, 1 mmol) and Na<sub>2</sub>CO<sub>3</sub> (1.25 g, 12 mmol) in water (30 mL) was heated in a water bath for approximately 2 hr until a clear solution was obtained. The solution was cooled and filtered. The filtrate was acidified with conc. HCl to give a yellow precipitate. The solids were collected and dried over night to give the desired product (1.86 g, 87%).

10

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 7.76 (m, 2H), 8.22 (m, 2H), 8.71 (d, 1H), 9.20 (d, 1H), 10.49 (s, 1H).

4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphthoic acid (step A):

- 15 To a solution of 3-chloro-4-hydroxybenzoic acid hydrazide (1.53 g, 8.23 mmol) in DMSO (20 mL) was added a solution of 4-formylnaphthoic acid (1.65 g, 8.23 mmol) in DMSO (2 mL). After stirring the solution for 16 hr, the reaction was diluted with ethyl acetate (30 mL) and water (30 mL). A precipitate formed. The precipitate was collected, washed with hexane and dried to give the product as a white solid in quantitative yield.

- 20 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 4.70 (d, 1H), 7.70 (m, 2H), 7.83 (d, 1H), 8.03 (m, 2H), 8.18 (d, 1H), 8.72 (s, 1H), 8.90 (d, 1H), 9.17 (s, 1H), 11.0 (brd s, 1H), 11.94 (s, 1H), 13.4 (brd s, 1H); MS (APCI, neg): 368.5, 370.2).

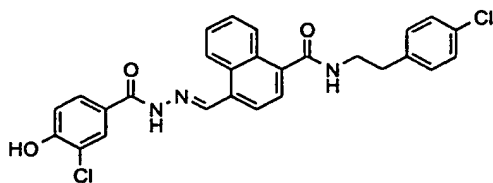
General procedure

- 25 Derivatives of 4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphthamides (step B):

- 30 To a solution of a derivative of 4-[(4-hydroxybenzoyl)-hydrazonomethyl]naphthoic acid in DMSO was added carbonyldiimidazole (1.2 eq). The solution was agitated for 5 minutes and diluted with DMSO to a concentration of 50 mM. The solution was then dispensed into 88 deep well plates containing solutions of amines in DMSO (50 mM). The plates were covered and agitated for 16 hours. The products were purified by HPLC.

The following compounds of formula XIII were prepared:

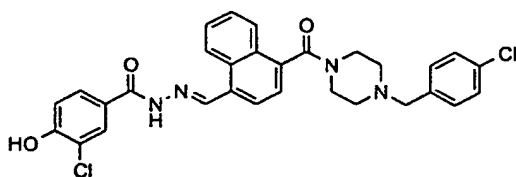
## EXAMPLE 455:



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.91 (t, 2H), 3.67 (t, 2H), 7.12 (d, 1H), 7.38 (qt, 4H), 7.58 (t, 2H), 7.70 (t, 1H), 7.50 (d, 1H), 7.95 (d, 2H), 8.03 (s, 1H), 8.69 (brd t, 1H), 8.81 (d, 1H), 9.12 (s, 1H), 11.02 (s, 1H), 11.89 (s, 1H); MS (APCI): 507.3, 508.5.

10

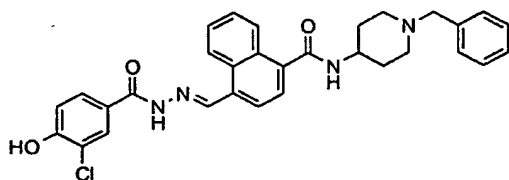
## EXAMPLE 456:



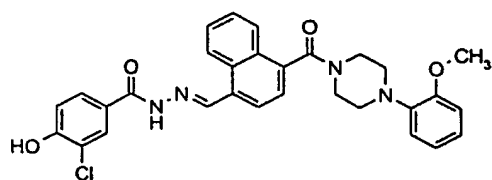
15

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.20 (brd m, 1H), 2.30 (brd m, 1H), 2.55 (m, 2H), 3.10 (brd m, 2H), 3.50 (s, 2H), 3.72 (brd m, 1H), 3.85 (brd m, 1H), 7.10 (d, 1H), 7.36 (qt, 4H), 7.53 (d, 1H), 7.70 (m, 2H), 7.82 (m, 2H), 7.95 (d, 1H), 8.03 (s, 1H), 8.88 (d, 1H), 9.11 (s, 1H), 11.00 (brd s, 1H), 11.89 (s, 1H); MS (APCI, neg.): 559.2, 561.2.

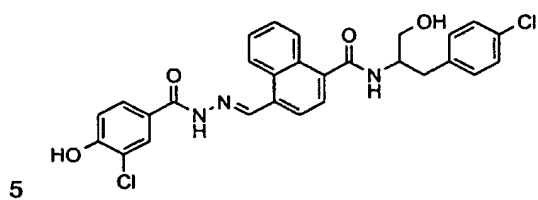
EXAMPLE 457:



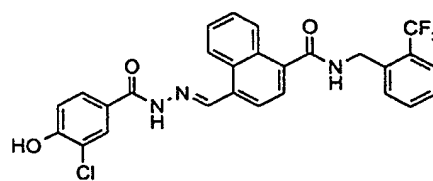
15 EXAMPLE 462:



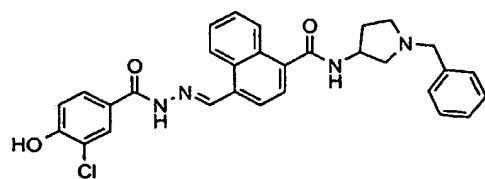
EXAMPLE 458:



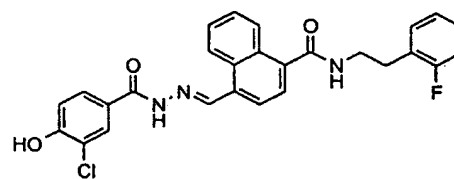
EXAMPLE 463:



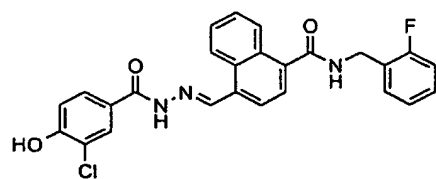
EXAMPLE 459:



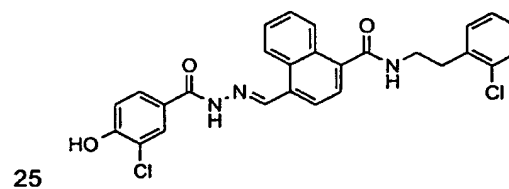
EXAMPLE 464:



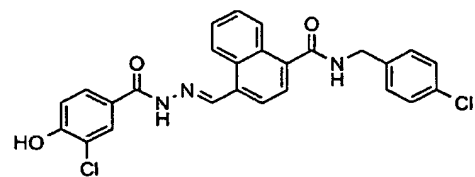
10 EXAMPLE 460:



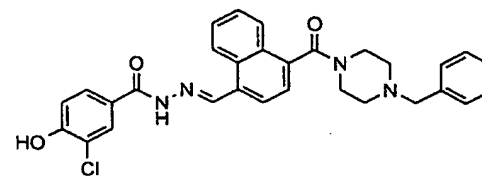
EXAMPLE 465:



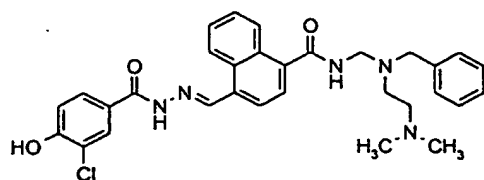
EXAMPLE 461:



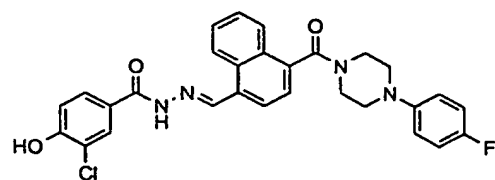
EXAMPLE 466:



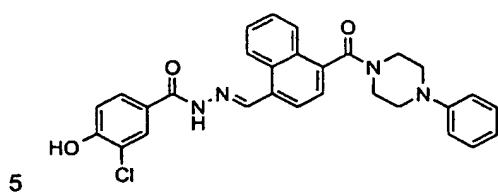
EXAMPLE 467:



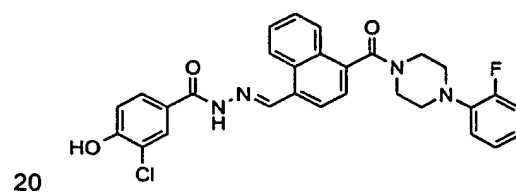
EXAMPLE 472:



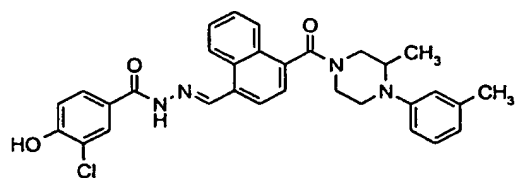
EXAMPLE 468:



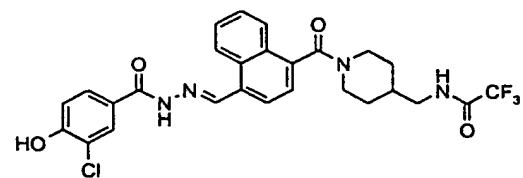
EXAMPLE 473:



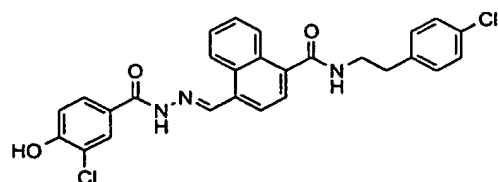
EXAMPLE 469:



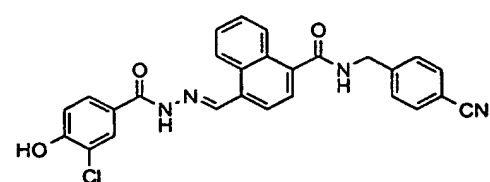
EXAMPLE 474:



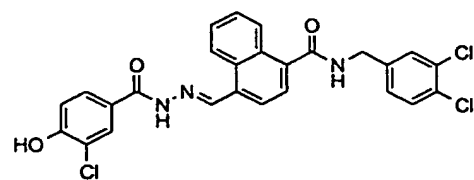
10 EXAMPLE 470:



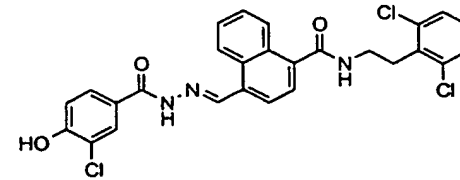
25 EXAMPLE 475:



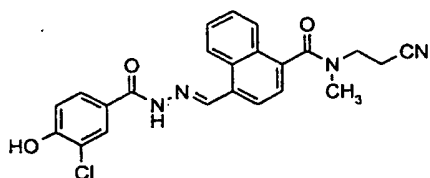
EXAMPLE 471:



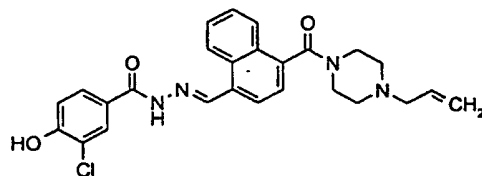
EXAMPLE 476:



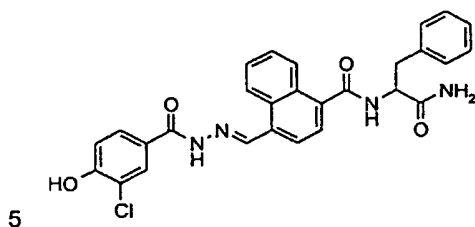
EXAMPLE 477:



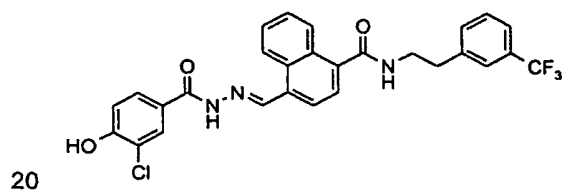
EXAMPLE 482:



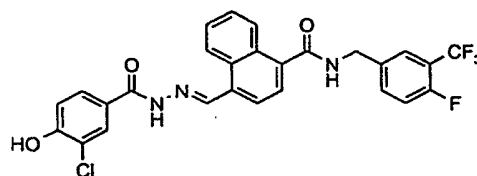
EXAMPLE 478:



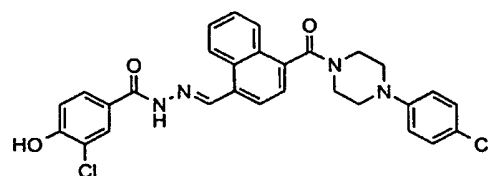
EXAMPLE 483:



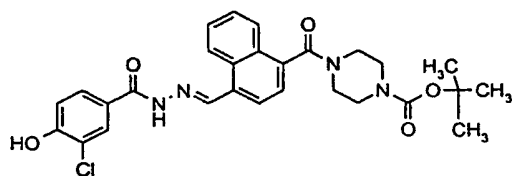
EXAMPLE 484:



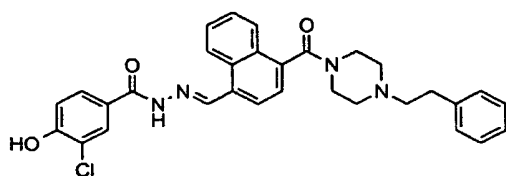
25 EXAMPLE 485:



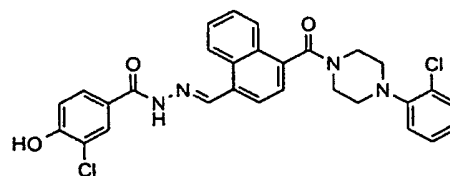
10 EXAMPLE 480:



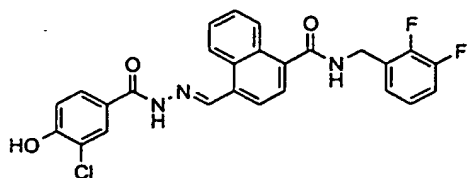
EXAMPLE 481:



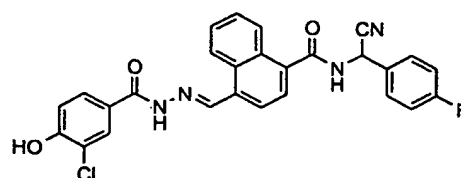
EXAMPLE 486:



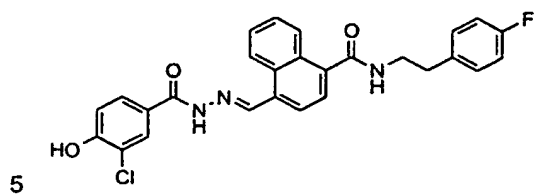
EXAMPLE 487:



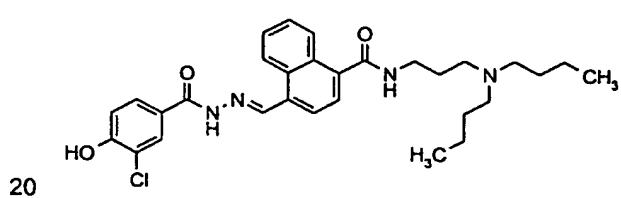
EXAMPLE 492:



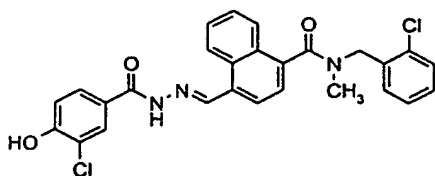
EXAMPLE 488:



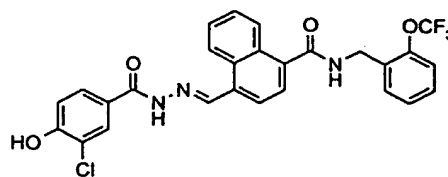
EXAMPLE 493:



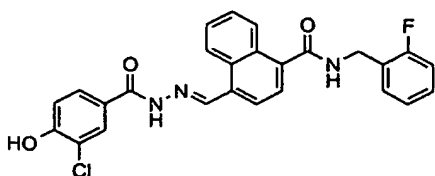
EXAMPLE 489:



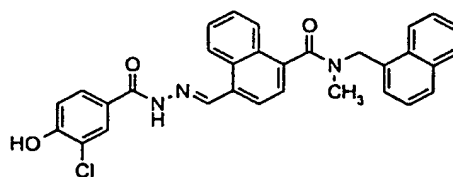
EXAMPLE 494:



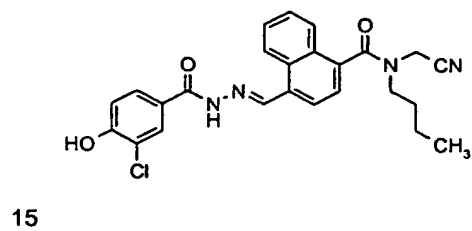
10 EXAMPLE 490:



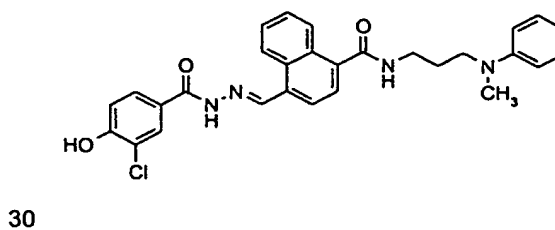
25 EXAMPLE 495:



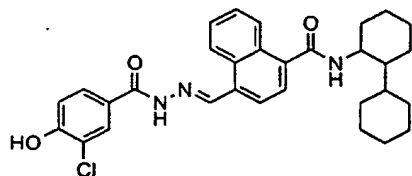
EXAMPLE 491:



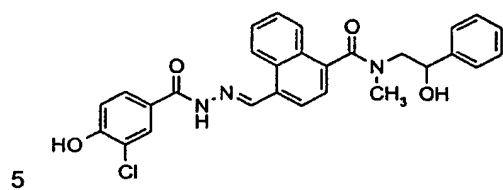
EXAMPLE 496:



EXAMPLE 497:

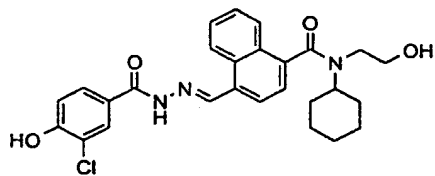


EXAMPLE 498:

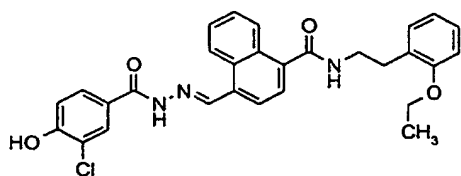


5

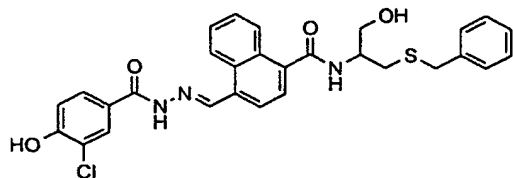
EXAMPLE 499:



10 EXAMPLE 500:



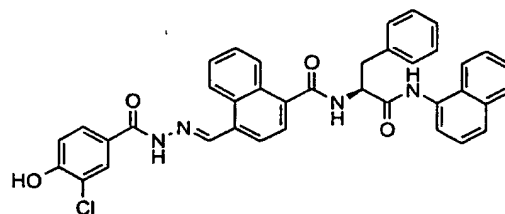
EXAMPLE 501:



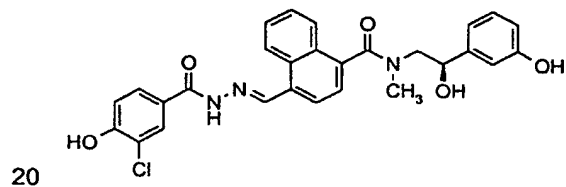
15

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EXAMPLE 502:

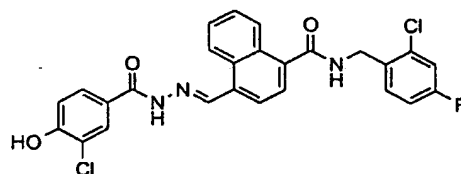


EXAMPLE 503:

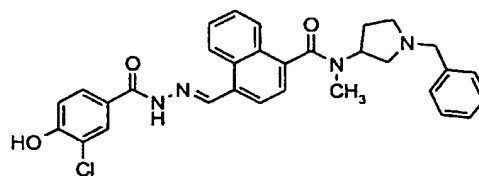


20

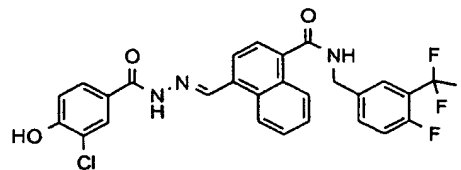
EXAMPLE 504:



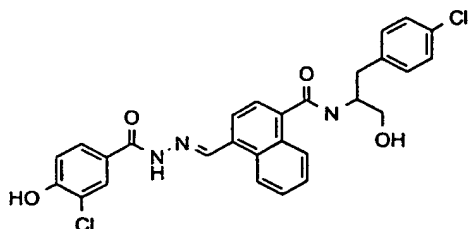
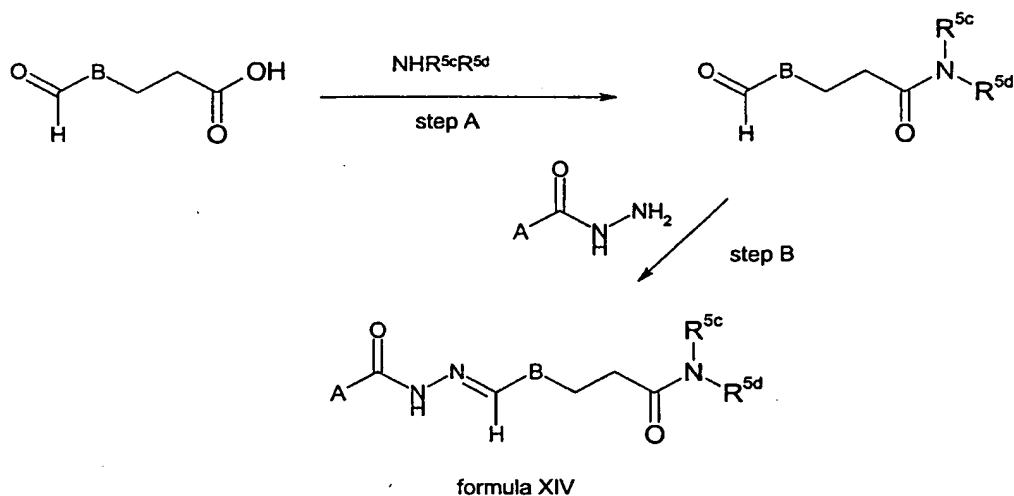
25 EXAMPLE 505:



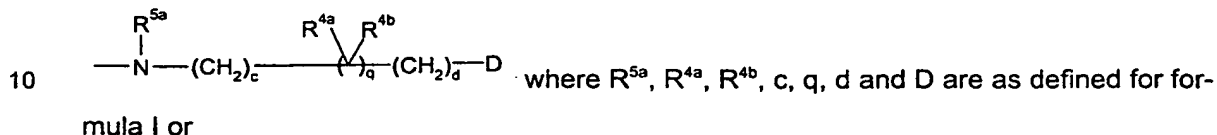
EXAMPLE 506:



## EXAMPLE 507:

5 General procedure for synthesis of compounds of the general formula XIV:

A and B are as defined for formula I and  $-NR^{5c}R^{5d}$  is



-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

- 15 Step A: The acid is coupled to a primary or secondary amine using one of the methods well-known to those skilled in the art. This coupling can be performed using one of the standard amide or peptide synthesis procedures such as by generating an active ester, an anhydride or

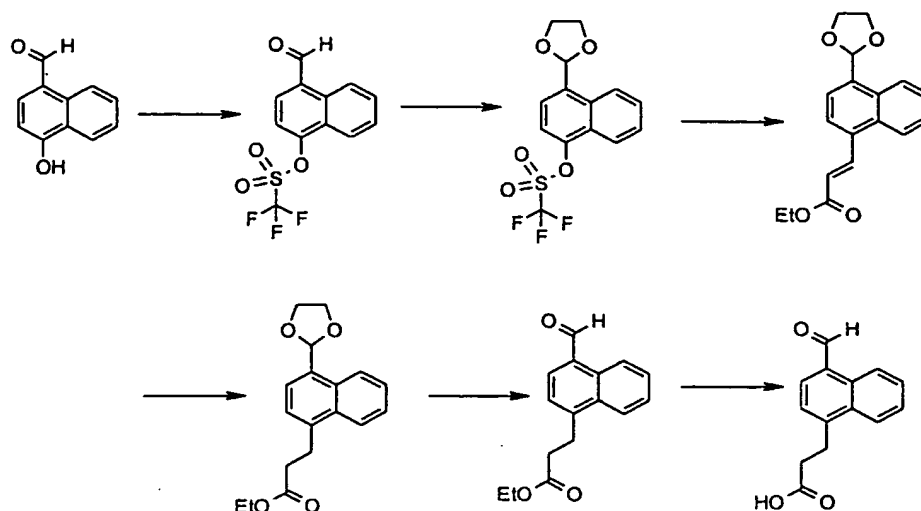
an acid halide that can then react with the amine to give a compound of formula XIV. The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either  
5 recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent giving a compound of formula XIV.

10

Step B: The carbonyl compounds are then treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, tert-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above  
15 solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N<sub>2</sub> or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product  
20 can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

25 Specific examples illustrating the preparation of compounds of the general formula XIV according to the invention are provided below.

The preparation of 3-(4-formylnaphthalene)propanoic acid is depicted below:



#### 4-Trifluoromethylsulfonyloxy naphthaldehyde:

To a solution of 4-hydroxy naphthaldehyde (34.4 g, 0.20 mol) in dichloromethane (200 mL) and pyridine (19 mL, 18.58 g, 0.23 mol) was added dropwise at 0°C trifluoromethane sulfo-  
 nic anhydride (46.75 g, 0.16 mol). The mixture was stirred at 0°C for 2 hr and at room tem-  
 perature for 16 hr. It was poured into water (200 mL), and extracted with ether (3 x 100 mL).  
 The combined organic extracts were washed with water (100 mL), 0.1 N hydrochloric acid (2  
 x 100 mL), water (100 mL), brine (100 mL), dried (MgSO<sub>4</sub>), and concentrated.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.89 - 7.97 (m, 3H), 8.09 (dd, J = 2.8, 6.5 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 9.24 (dd, J = 2.8, 6.5 Hz, 1H), 10.45 (s, 1H).

#### 2-(4-Trifluoromethylsulfonyloxy naphthyl) dioxolane:

A solution of 4-trifluoromethylsulfonyloxy naphthaldehyde (4.09 g, 13.4 mmol), ethylene gly-  
 col (1.5 mL, 1.67 g, 26.9 mmol), and p-toluene sulfonic acid (250 mg) in toluene (250 mL)  
 was refluxed for 16 hr using a Dean -Stark trap. The solution was allowed to reach room  
 temperature, was washed with satd. NaHCO<sub>3</sub>-sol. (2x 80 mL), brine (80 mL), dried (MgSO<sub>4</sub>),  
 and concentrated to give a yellow oil (4.79 g, quant).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.19 (m, 4H), 6.47 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.66- 7.70 (m, 2H),  
 7.81 (d, J = 8.0 Hz, 1H), 8.13 (dd, J = 3.3, 6.3 Hz, 1H), 8.30 (dd, J = 3.3, 6.3 Hz, 1H).

GCMS: 348.

2-[4-(2-ethoxycarbonylvinyl)naphthyl]dioxolane:

Nitrogen was passed through a solution of 2-(4-trifluoromethylsulfonyloxynaphthyl) dioxolane  
5 (2.46 g, 7.06 mmol), ethyl acrylate (2.3 mL, 2.1 g, 21.2 mmol), triethylamine (4.3 g, 42.3  
mmol) in DMF (6 mL) for 15 min, and bis(triphenylphosphine)palladium dichloride was ad-  
ded. The well stirred solution was heated at 90°C for 8 hr, and concentrated. The residue  
was dissolved in ethyl acetate (50 mL), washed with brine (2x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and  
concentrated. Purification by flash chromatography using hexane /ethyl acetate 9:1 as elu-  
10 ent provided a yellow solid (1.13 g, 53%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.38 (t, J = 7.0 Hz, 3H), 3.74 - 4.22 (m, 4H), 8.65 (q, J = 7.0 Hz, 2H), 6.50  
(s, 1H), 6.53 (d, J = 15.7 Hz, 1H), 7.58-7.62 (m, 2H), 7.74 (d, J = 7.5 Hz, 1H), 7.80 (d, J =  
7.5 Hz, 1H), 8.21-8.28 (m, 2H), 8.52 (d, J = 15.2 Hz, 1H).

15

2-[4-(2-ethoxycarbonylethyl)naphthyl]dioxolane:

To a solution of 2-[4-(2-ethoxycarbonylvinyl)naphthyl]dioxolane (701 mg, 2.35 mmol) in ethyl  
acetate (15 mL) was added palladium (5% on BaCO<sub>3</sub>, 51 mg). The mixture was stirred under  
a hydrogen atmosphere for 16 hr, filtered by suction through Celite and concentrated to pro-  
vide 689 mg (98%) of a colorless oil.

20

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, J = 7.0 Hz, 3H), 2.75 (t, J = 8.0 Hz, 2H), 3.43 (t, J = 8.0 Hz, 2H),  
4.12- 4.22 (m, 6H), 6.46 (s, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.54 - 7.70 (m, 2H), 7.70 (d, J =  
7.3 Hz, 1H), 8.07 (dd, J = 3.3, 6.5 Hz, 1H), 8.26 (dd, J = 3.3, 6.5 Hz, 1H).

25

Ethyl 3-(4-formylnaphthalene)propanoic acid:

To a solution of 2-[4-(2-ethoxycarbonylethyl)naphthyl]dioxolane (689 mg, 2.29 mmol) in THF  
(15 mL) was added 6N hydrochloric acid (2 mL). The mixture was stirred for 16 hr at room  
temperature, diluted with ethyl acetate (20 mL), washed with satd. NaHCO<sub>3</sub> solution (20  
30 mL), dried (MgSO<sub>4</sub>), and concentrated to give the product as a colorless oil (407 mg, 68%)  
that crystallized upon sitting.

3-(4-formylnaphthalene)propanoic acid:

Ethyl 3-(4-formylnaphthalene)propanoic acid (310 mg, 1.2 mmol) was suspended in water (10 mL), and  $\text{Na}_2\text{CO}_3$  (130 mg, 1.2 mmol) was added. The mixture was refluxed for 5 hr, and allowed to cool to room temperature. After acidification with conc. hydrochloric acid, a precipitate was formed. The precipitate was collected by suction, and dried at 80°C in vacuum for 16 hr to give a white solid (300 mg, 73%).

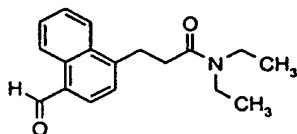
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  2.69 (t,  $J = 7.0$  Hz, 2H), 3.39 (t,  $J = 7.0$  Hz, 2H), 7.66-7.77 (m, 2H), 8.10 (d,  $J = 7.3$  Hz, 1H), 8.23 (dd,  $J = 1.1, 8.0$  Hz, 1H), 9.22 (dd,  $J = 1.1, 9.0$  Hz, 1H), 10.33 (s, 1H), 12.30 (br s, 1H).

General procedure (Step A):

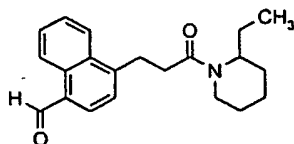
Preparation of 3-(4-formylnaphthalene)propanamides:

To a solution of 3-(4-formylnaphthalene)propanoic acid (100 mg, 0.437 mmol) in DMF (3 mL) was added carbonyl diimidazole (140 mg, 0.863 mmol). The mixture was stirred at room temperature for 1 hr, and amine (1.3 equivalents) was added. After stirring at room temperature for 16 hr, the mixture was diluted with ethylacetate (5 mL), extracted with water (5 mL), 1 N hydrochloric acid (5 mL), and water (3 x 5 mL), dried ( $\text{MgSO}_4$ ) and concentrated. After flash chromatography using hexane/ethylacetate 1 : 1 pure amide was isolated.

Examples of amides:



$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.06 (t,  $J = 7.0$  Hz, 3H), 1.12 (t,  $J = 7.0$  Hz, 3H), 2.79 (t,  $J = 8.0$  Hz, 2H), 3.50 (t,  $J = 8.0$  Hz, 2H), 4.12 (q,  $J = 7.1$  Hz, 2H), 7.54 (d,  $J = 7.3$  Hz, 1H), 7.64 - 7.71 (m, 2H), 7.92 (d,  $J = 7.3$  Hz, 1H), 8.18 (dd,  $J = 1.3, 8.0$  Hz, 1H), 9.34 (dd,  $J = 1.3, 8.0$  Hz, 1H), 10.34 (s, 1H). MS (APCI, pos.) 284.1



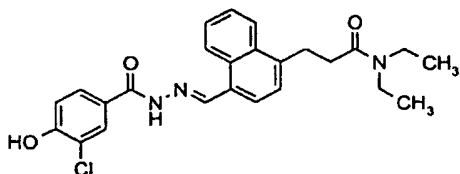
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.77 (t, J = 7.0 Hz, 3 H), 0.86 (t, J = 7.0 Hz, 3 H), 1.15 -1.82 (m, 8 H),  
2.58 (dt, 0.5 H), 2.65 - 2.88 (m, 2H), 2.92 (dt, 0.5H), 3.39 - 3.60 (m, 2.5H), 3.62- 3.73 (m,  
5 0.5H), 4.58 (dd, 0.5H), 4.73 (m, 0.5H), 7.56 (d, J = 7.3 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H),  
7.61 - 7.72 (m, 2H), 8.16 (d, J = 8.3 Hz, 1H), 9.33 (d, J = 8.0 Hz, 1H), 10.34 (s, 1H). MS  
(APCI, pos.) 325.2

Derivatives of 4-[(4-hydroxybenzoyl)hydrazonomethyl]naphthylpropanamides (step B):

10

These compounds were prepared according to the general procedure for the synthesis of  
alkylidene hydrazones from the condensation of 4-formyl-1-naphthyl propanamides (from  
step A) and 4-hydroxybenzoic acid hydrazide derivatives.

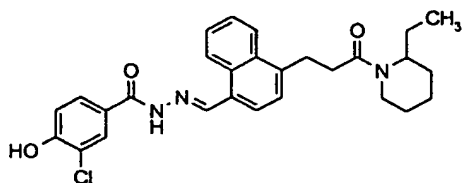
15 EXAMPLE 508:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 0.95 - 1.02 (m, 6H), 2.69 (t, J = 7.3 Hz, 2H), 3.19 (q, J = 7.0 Hz, 2H),  
3.25 (q, J = 7.0 Hz, 2H), 3.33 (t, J = 7.3 Hz, 2H), 7.08 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 7.5  
20 Hz, 1H), 7.65 (m, 2H), 7.81 (m, 2H), 8.00 (d, J = 2.0 Hz, 1H), 9.17 (dd, J = 2.4, 6.5 Hz, 1H),  
8.87 (d, J = 7.6 Hz, 1H), 9.05 (s, 1H), 11.00 (s, 1H), 11.77 (s, 1H). MS (APCI, pos. ): 452.2,  
454.2

25

## EXAMPLE 509:

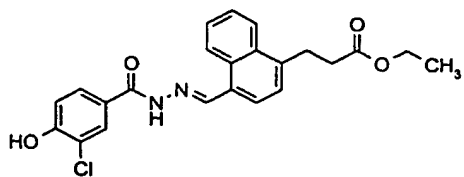


- 5  $^1\text{H}$  NMR (DMSO- $\text{D}_6$ )  $\delta$  0.68 (t,  $J$  = 7.5 Hz, 3H), 0.75 (t,  $J$  = 7.5 Hz, 3H), 0.76 (dd, 0.5 H), 0.90 (dd, 0.5 H), 1.02 - 1.68 (m, 8H), 2.49 (m, 0.5H), 2.75 (m, 2H), 2.90 (t,  $J$  = 14.0 Hz, 0.5H), 3.33 (m, 2H), 3.61 (d,  $J$  = 12.0, Hz, 0.5H), 3.75 (m, 0.5H), 4.36 (d,  $J$  = 12.0 Hz, 0.5H), 4.53 (m, 0.5H), 7.08 (d,  $J$  = 8.5 Hz, 1H), 7.50 (d,  $J$  = 7.5 Hz, 1H), 7.64 - 7.66 (m, 2H), 7.80 (dd,  $J$  = 1.9, 8.5 Hz, 1), 7.83 (d,  $J$  = 7.5 Hz, 1H), 8.00 (d,  $J$  = 1.9, Hz, 1H), 8.17 (m, 1H), 8.88 (d,  $J$  = 7.5 Hz, H), 7.25 (s, 1H), 11.0 (s, 1H), 11.76 (s, 1H). MS (APCI, pos.): 492.1, 494.1
- 10

## EXAMPLE 510:

Ethyl 4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl propanoate

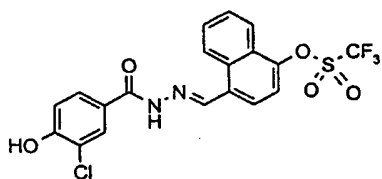
15



- The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of ethyl 4-formyl-1-naphthylpropanoate (from step E) and 3-chloro-4-hydroxy benzoic acid hydrazide.
- 20

- $^1\text{H}$  NMR (DMSO- $\text{D}_6$ )  $\delta$  1.14 (t,  $J$  = 7.0 Hz, 3H), 2.73 (t,  $J$  = 7.5 Hz, 2H), 3.35 (t,  $J$  = 7.5 Hz, 2H), 4.02 (q,  $J$  = 7.0 Hz, 2H), 7.08 (d,  $J$  = 8.6 Hz, 1H), 7.66 (m, 2H), 7.79 (dd,  $J$  = 1.8, 8.6 Hz, 1H), 7.86 (d,  $J$  = 7.5 Hz, 1H), 8.85 (d,  $J$  = 7.7 Hz, 1H), 9.05 (s, 1H), 11.0 (brd s, 1H), 11.78 (s, 1H). MS (APCI, pos.): 425.5, 427.3
- 25

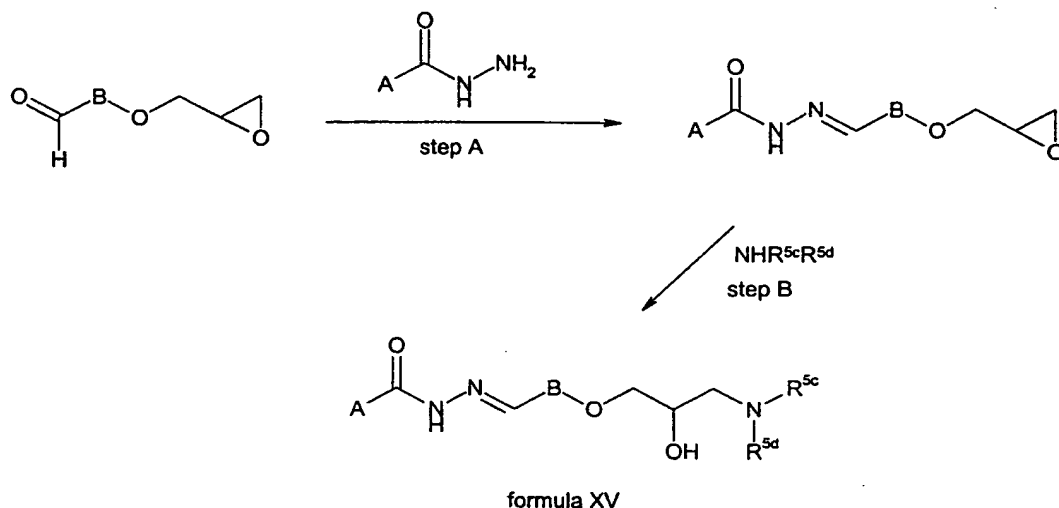
## EXAMPLE 511:

5 3-Chloro-4-hydroxy benzoic acid (4-trifluoromethylsulfonyloxy naphthylidene) hydrazide

10 The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-trifluoromethylsulfonyloxy naphthaldehyde 3-chloro-4-hydroxy benzoic acid hydrazide.

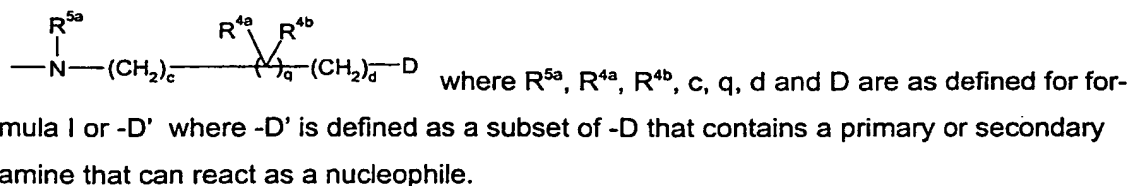
$^1\text{H}$  NMR (DMSO- $\text{D}_6$ )  $\delta$  7.09 (d,  $J = 8.7$  Hz, 1H), 7.68 - 7.95 (m, 4H), 8.00 - 8.10 (m, 3H), 8.90 (s, 1H), 9.10 (s, 1H), 11.02 (s, 1H), 11.96 (s, 1H). MS (APCI, pos.): 473.2, 475.1

General procedure for synthesis of compounds of the general formula XV:



5

A and B are as defined for formula I and  $-NR^{5c}R^{5d}$  is



10

Step A: The carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of  $N_2$  or Ar at temperatures between  $0^\circ\text{C}$  to  $140^\circ\text{C}$ , preferably between  $10^\circ\text{C}$  to  $80^\circ\text{C}$ . In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column

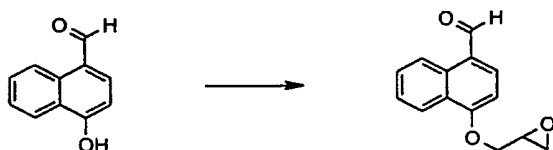
20

chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

Step B: The epoxide is then ring opened by a primary or secondary amine using one of the methods well-known to those skilled in the art to give a compound of formula XV. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, DMF, NMP, water or a compatible mixture of two or more of the above solvents. The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent giving a compound of formula XV.

Specific examples illustrating the preparation of compounds of the general formula XV according to the invention are provided below.

The preparation of 4-(2,3-epoxypropoxy)-1-naphthaldehyde is depicted below:



25

4-(2,3-epoxypropoxy)-1-naphthaldehyde:

To a solution of 4-hydroxy-1-naphthaldehyde (1 g, 5.8 mmol) in DMSO (20 mL) was added  $K_2CO_3$  (1 g, 7.2 mmol). The mixture was stirred at room temperature for 30 min, and then 2,3-epoxypropyl bromide (0.96 g, 7 mmol) was added. After stirring for 24 hr, water (100

mL) was added. The mixture was extracted with ethyl acetate (3x80 mL), dried ( $\text{MgSO}_4$ ), and concentrated to give a brown solid (1.23 g, 93%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.88 (dd,  $J = 2.6, 4.8$  Hz, 1H), 3.02 (dd,  $J = 4.0, 4.6$  Hz, 1H), 3.51 - 3.57 (m, 1H), 4.22 (dd,  $J = 5.8, 11.1$  Hz, 1H), 4.55 (dd,  $J = 2.8, 11.1$  Hz, 1H), 6.94 (d,  $J = 8.1$  Hz, 1H), 7.60 (t,  $J = 7.2$  Hz, 1H), 7.71 (t,  $J = 7.7$  Hz, 1H), 7.92 (d,  $J = 8.0$  Hz, 1H), 8.89 (d,  $J = 8.4$  Hz, 1H), 9.31 (d,  $J = 8.6$  Hz, 1H), 10.22 (s, 1H).

General Procedure:

4-hydroxybenzoic acid 4-(2,3-epoxypropanoxy)-1-naphthylidene hydrazide derivatives (step A):

The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the above epoxy-aldehyde with 4-hydroxy benzoic acid hydrazide derivatives.

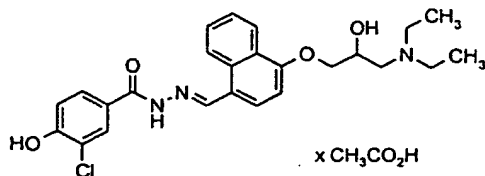
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  2.84 (dd,  $J = 2.2, 4.9$  Hz, 1H), 2.92 (dd,  $J = 4.5, 4.5$  Hz, 1H), 3.45 - 3.57 (m, 1H), 4.11 (dd,  $J = 6.4, 11.3$  Hz, 1H), 4.60 (d,  $J = 11.3$  Hz, 1H), 7.02 - 7.18 (m, 2H), 7.55 - 7.90 (m, 4H), 7.99 (d,  $J = 1.9$  Hz, 1H), 8.29 (d,  $J = 8.3$  Hz, 1H), 8.90 - 9.05 (d, 2H), 10.94 (s, 1H), 11.66 (s, 1H). MS (APCI, negative): 395.

General procedure for epoxide ring opening (step B):

A mixture of epoxide (0.2 mmol) and amine (0.3 mmol) in 10 mL ethanol was refluxed for 4 hr. A red oil was obtained after concentration. Products were purified by preparatory HPLC.

Examples of compounds of formula XV:

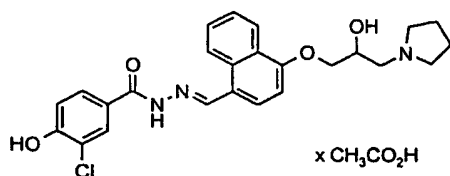
EXAMPLE 512:



$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  0.95 (t,  $J$  = 6.9 Hz, 6H), 1.90 (s, 3H), 2.50, 2.62 (2q,  $J$  = 6.6 Hz, 4H), 2.70 (dd,  $J$  = 6.6, 13.0 Hz, 1H), 2.88 (dd,  $J$  = 7.0, 14.2 Hz, 1H), 3.95 - 4.35 (m, 3H), 7.02 (d,  $J$  = 8.7 Hz, 1H), 7.06 (d,  $J$  = 8.3 Hz, 1H), 7.55 - 7.85 (m, 4H), 7.96 (d,  $J$  = 1.9 Hz, 1H), 8.36 (d,  $J$  = 8.3 Hz, 1H), 8.85 - 9.05 (d, 2H), 11.60 (s, 1H); MS (APCI, pos.): 470.

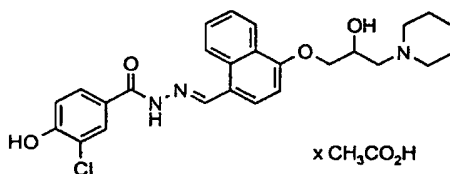
5

## EXAMPLE 513:



$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.67 (brd s, 4H), 1.88 (s, 3H), 2.50 - 2.85 (m, 6H), 4.0 - 4.3 (m, 3H), 7.00 - 7.12 (t, 2H), 7.55 - 7.85 (m, 4H), 7.97 (s, 1H), 8.36 (d,  $J$  = 8.3 Hz, 1H), 8.85 - 9.05 (d, 2H), 11.63 (s, 1H); MS (APCI, pos.): 468.

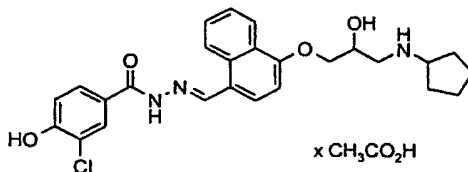
## EXAMPLE 514:



15

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.30 - 1.55 (m, 6H), 1.88 (s, 3H), 2.35 - 2.60 (m, 6H), 4.05 - 4.30 (m, 3H), 7.04 (d,  $J$  = 8.5 Hz, 1H), 7.12 (d,  $J$  = 8.3 Hz, 1H), 7.55 - 7.85 (m, 4H), 7.97 (d,  $J$  = 2.1 Hz, 1H), 8.36 (d,  $J$  = 8.2 Hz, 1H), 8.85 - 9.05 (d, 2H), 11.62 (s, 1H); MS (APCI, pos.): 470.

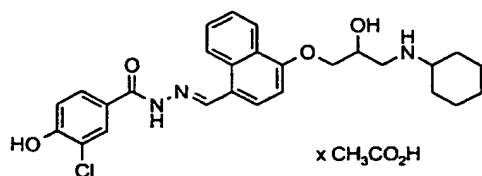
## 20 EXAMPLE 515:



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.25 -1.82 (m, 8H), 1.88 (s, 3H), 2.68 -2.90 (m, 2H), 3.08 (m, 1H), 4.0 - 4.25 (m, 3H), 7.03 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.52 - 7.85 (m, 4H), 7.97 (d, J = 1.4 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.85 - 9.0 (d, 2H), 11.61 (s, 1H); MS (APCI, pos.): 482.

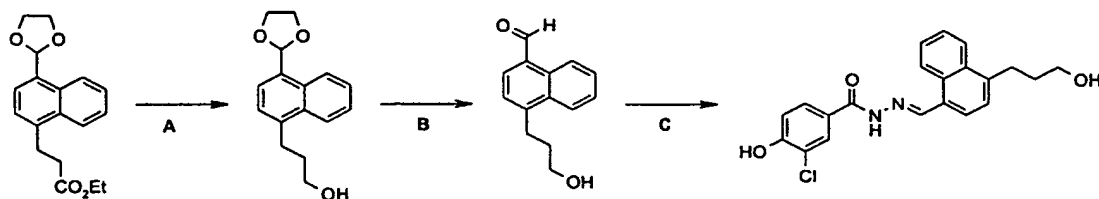
5

## EXAMPLE 516:



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.95 -1.80 (m, 10H), 1.88 (s, 3H), 2.45 (m, 1H), 2.70 -2.90 (m, 2H), 3.98-4.30 (m, 3H), 7.02 (d, J = 8.52 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 7.52 -- 7.75 (m, 4H), 7.97 (d, J = 2.05 Hz, 1H), 8.34 (d, J = 8.33 Hz, 1H), 8.87 - 9.00 (m, 2H), 11.61 (s, 1H); MS (APCI, pos.): 496.

## EXAMPLE 517:

15 3-Chloro-4-hydroxybenzoic acid 4-(3-hydroxypropyl)naphthylmethylenesulfonylhydrazide

## 2-[4-(3-Hydroxypropyl)naphthyl]dioxolane (step A):

To a solution of 2-[4-(2-ethoxycarbonyl)ethyl]naphthyl]dioxolane (210 mg, 0.70 mmol) in anhydrous THF (5 mL) was added at 0°C 1M lithium aluminum hydride in THF (0.5 mL). THF (5 mL) was added and the mixture was stirred at room temperature for 16 hr, diluted with water (10 mL), acidified with conc. hydrochloric acid, and extracted with ether (3x 10 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography using hexane/ethyl acetate 2:1 as eluent to provide 67 mg (37 %)

25 of a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.51 (brd s, 1H), 1.99 - 2.04 (m, 2H), 3.19 (t, J = 7.4 Hz, 2H), 3.75 (t, J = 6.3 Hz, 2H), 4.16 - 4.22 (m, 4H), 6.47 (s, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.52 - 7.70 (m, 2H), 7.70 (d, J = 7.3 Hz, 1H), 8.11 (d, J = 9.8 Hz, 1H), 8.25 (d, J = 9.8 Hz, 1H). GCMS: 258

5

1-Formyl-4-(3-hydroxypropyl)naphthalene (step B):

To a solution of 2-[4-(3-hydroxypropyl)naphthyl]dioxolane (67 mg, 0.26 mmol) in anhydrous THF (5 mL) was added 1N hydrochloric acid (1 mL). The mixture was stirred at room temperature for 48 hr, diluted with ethyl ether (20 mL), washed with satd. NaHCO<sub>3</sub> solution (2x 10 mL), dried (MgSO<sub>4</sub>), concentrated and coevaporated with CHCl<sub>3</sub> (3 x 10 mL) to yield 40 mg (72%) of a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.56 (brd s, 1 H), 2.02 - 2.08 (m, 2H), 3.27 (t, J = 7.5 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 7.53 (d, J = 7.3 Hz, H), 7.62 - 7.70 (m, 2H), 7.92 (d, J = 7.3 Hz, 1H), 9.17 (d, J = 8.3 Hz, 1H), 9.34 (d, J = 8.6 Hz, 1H), 10.34 (s, 1H).

15

3-Chloro-4-hydroxybenzoic acid 4-(3-hydroxypropyl)naphthylmethylene hydrazide (step C):

This compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones by condensation of 1-formyl-4-(3-hydroxypropyl) naphthalene from step B and 3-chloro-4-hydroxy benzoic acid hydrazide.

20

<sup>1</sup>H NMR DMSO-D<sub>6</sub>) δ 1.83 (m, 2H), 3.12 (t, J = 7.5 Hz, 2H), 3.51 (dt, J = 4.9, 7.0 Hz, 2H), 7.09 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.65 (m, 2H), 7.80 (dd, J = 2.0, 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 2.5, 7.0 Hz, 1H), 8.84 (d, J = 8.4 Hz, 1H), 9.05 (s, 1H), 10.98 (s, 1H), 11.76 (s, 1H).

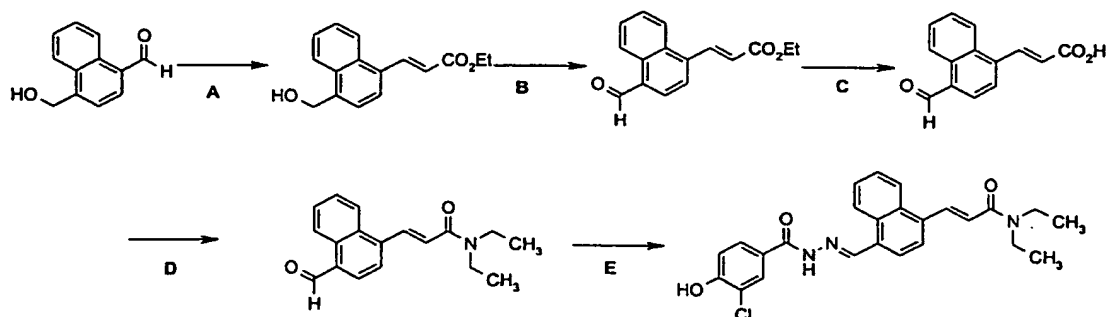
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MS (APCI, pos.): 383.1, 385.1.

EXAMPLE 518:

4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl diethylacrylamide

30



Ethyl (4-hydroxymethyl) naphthalene acrylate (step A):

To a suspension of sodium hydride (160 mg, 60% dispersion in mineral oil, 4.00 mmol) in THF (10 mL) at 0°C was added triethylphosphonoacetate (0.77 mL, 670 mg, 3.88 mmol).

- 5 The mixture was stirred at 0°C for 1 hr, and 4-hydroxymethyl naphthaldehyde (600 mg, 3.2 mmol) in THF (5 mL) was added at the same temperature. The mixture was stirred at room temperature for 16 hr, diluted with satd.  $\text{NH}_4\text{Cl}$ -solution (10 mL), and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated, to provide 900 mg of a colorless oil, which was used without further purification in the next
- 10 step.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.37 (t,  $J = 7.1$  Hz, 3H), 1.86 (brd s, 1H), 4.32 (q,  $J = 7.1$  Hz, 2H), 5.17 (s, 2H), 6.50 (d,  $J = 15.7$  Hz, 1H), 7.54 - 7.62 (m, 2H), 7.70 (d,  $J = 7.4$  Hz, 1H), 8.13 (dd,  $J = 2.8, 9.8$  Hz, 1H), 8.21 (dd,  $J = 2.8, 9.8$  Hz, 1H), 8.49 (d,  $J = 15.7$  Hz, 1H).

15

Ethyl 4-formylnaphthalene acrylate (step B):

The crude material (900 mg) from step A was dissolved in chloroform (10 mL), and manganese dioxide (1.5 g, 17 mmol) was added. After stirring at room temperature for 16 h, the suspension was filtered by suction through Celite, and the filtrate was concentrated.

- 20 Flash chromatography using hexane/ethyl acetate 5:1 provided 491 mg (60% over 2 steps) of a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.39 (t,  $J = 7.1$  Hz, 3H), 1.86 (brd s, 1H), 4.34 (q,  $J = 7.1$  Hz, 2H), 6.60 (d,  $J = 15.7$  Hz, 1H), 7.68 - 7.75 (m, 2H), 7.85 (d,  $J = 7.4$  Hz, 1H), 8.00 (d,  $J = 7.4$  Hz, 1H), 8.25 (d,  $J = 8.1$  Hz, 1H), 8.50 (d,  $J = 15.7$  Hz, 1H), 9.31 (dd,  $J = 1.3, 8.1$  Hz, 1H), 10.43 (s, 1H). MS (APCI, neg.): 254.1

25

#### 4-Formylnaphthalene acrylic acid (step C):

A suspension of ethyl 4-formylnaphthalene acrylate (391 mg, 1.53 mmol), sodium carbonate (195 mg, 1.84 mmol) in water (10 mL) was refluxed for 16 hr. The cold solution was filtered, and the filtrate was acidified with conc. hydrochloric acid. The precipitate was collected by suction and dried for 48 hr in vacuum to give the product (325 mg, 94%) as a yellow solid.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 6.72 (d, J = 15.7 Hz, 1H), 7.71 - 7.75 (m, 2H), 8.12 (d, J = 7.45 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 15.7 Hz, 1H), 9.21 (d, J = 8.0 Hz, 1H), 10.43 (s, 1H).

#### 4-Formylnaphthalene diethyl acrylamide (step D):

To a solution of 4-formylnaphthalene acrylic acid (210 mg, 0.92 mmol) in DMF (4 mL) was added carbonyl diimidazole (180 mg, 1.10 mmol). The mixture was stirred at room temperature for 1 hr, and diethylamine (0.1 mL, 71 mg, 0.97 mmol) was added. After stirring at room temperature for 16 hr, the mixture was diluted with ethylacetate (5 mL), extracted with water (5 mL), 1 N hydrochloric acid (5 mL), and water (3 x 5 mL), dried (MgSO<sub>4</sub>) and concentrated. After flash chromatography using hexane/ethylacetate 1 : 1, 115 mg (43%) of a yellow oil was obtained.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.55 (m, 4H), 6.97 (d, J = 15.7 Hz, 1H), 7.63 - 7.76 (m, 2H), 7.80 (d, J = 7.4 Hz, 1H), 7.99 (d, J = 7.4 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.51 (d, J = 15.7 Hz, 1H), 9.30 (d, J = 8.3 Hz, 1H), 10.43 (s, 1H).

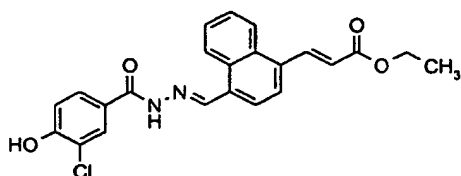
#### 4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl diethylacrylamide (step E):

The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-naphthyl diethylacrylamide (from step D) and 3-chloro-4-hydroxy benzoic acid hydrazide.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 1.11 (t, J = 7.0 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H), 3.42 (q, J = 7.0 Hz, 1H), 3.56 (q, J = 7.0 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 15.1 Hz, 1H), 7.67 - 7.72 (m, 2H), 7.81 (d, J = 8.3 Hz, 1H), 7.96-8.03 (m, 2H), 8.06 (d, J = 7.7 Hz, 1H), 8.26 (dd, J =

2.1, 7.2 Hz, 1H), 8.32 (d, J = 15.1 Hz, 1H), 8.83 (d, J = 7.0 Hz, 1H), 9.13 (s, 1H), 11.00 (s, 1H), 11.86 (s, 1H). MS (APCI, pos.): 450.3

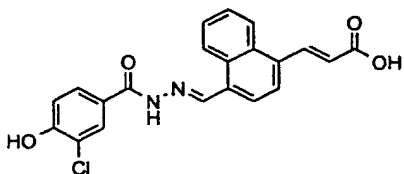
## EXAMPLE 519:

5 Ethyl 4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl acrylate

10 The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of ethyl 4-formyl-1-naphthyl acrylate (from step B) and 3-chloro-4-hydroxy benzoic acid hydrazide.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 1.29 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 6.75 (d, J = 15.7 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.71 (m, 2H), 7.92 (d, J = 8.5 Hz, 1H), 8.01 (m, 2H), 8.07 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 15.7 Hz, 1H), 8.81 (d, J = 7.1 Hz, 1H), 9.13 (s, 1H), 11.00 (s, 1H), 11.89 (s, 1H). MS (APCI, pos.): 421.1, 423.0

## EXAMPLE 520:

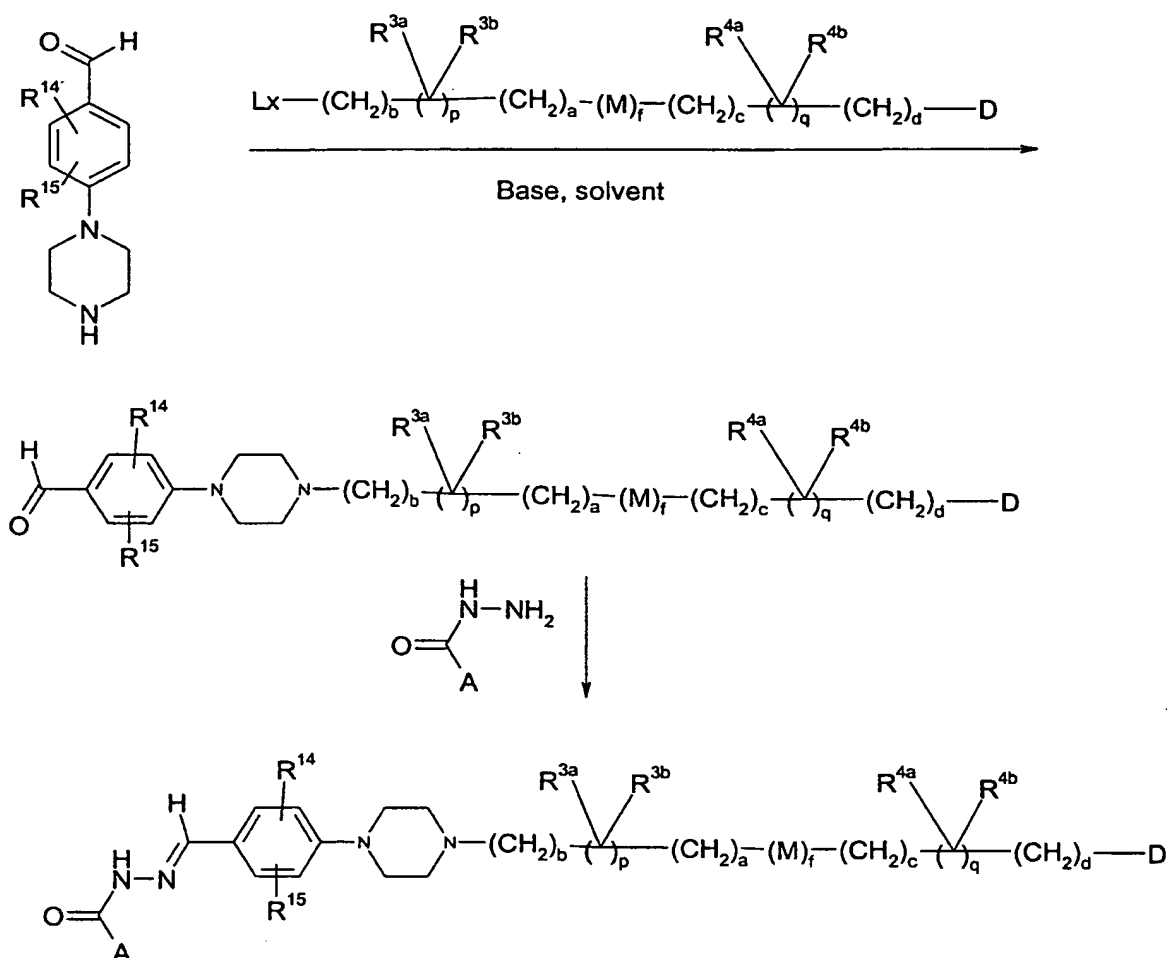
20 4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl acrylate

25 The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl -1-naphthyl acrylate (from step C) and 3-chloro-4-hydroxy benzoic acid hydrazide.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 6.65 (d, J = 15.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 7.66 - 7.74 (m, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.97 - 8.05 (m, 3H), 8.29 (dd, J = 2.2, 7.1 Hz, 1H), 8.41 (d, J = 15.6 Hz, 1H), 8.82 (d, J = 7.6 Hz, 1 H), 9.12 (s, 1 H), 10.92 (s, 1 H), 11.89 (s, 1H), 12.62 (s, 1H). MS (APCI, pos.): 394.1, 395.3

General procedure for the synthesis of substituted piperazine-aryl-aldehydes followed by hydrazone formation:

- 10 The substituted piperazine-aryl-aldehydes may be prepared by N-alkylation of the corresponding unsubstituted piperazine-aryl-aldehydes using various electrophilic alkylating agents that introduce the -(K)<sub>m</sub>-D moiety as defined above.



wherein Lx is a leaving group such as -Cl, -Br, -I, -OSO<sub>2</sub>CH<sub>3</sub>, -OSO<sub>2</sub>p-tolyl or -OSO<sub>2</sub>CF<sub>3</sub>; and A, R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup>, a, b, c, d, f, p, q, D, M, R<sup>14</sup> and R<sup>15</sup> are as defined for formula I.

5

According to the above scheme the substituted piperazine-aryl-aldehydes can be prepared by stirring piperazinylbenzaldehydes or piperazinyl-naphthaldehydes in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, DMSO, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, water or a compatible mixture of two or more of the above solvents with an equimolar amount of an alkyl halide or an aryl-lower alkyl halide and in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or

10

potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-collidine or benzyl-dimethyl- ammonium methoxide or hydroxide. The reaction can be performed at 0°C to 150°C, preferably at 20°C to 100°C and preferably in an inert atmosphere of N<sub>2</sub> or Ar. When the reaction is complete the mixture is filtered, concentrated in vacuo and the resulting product optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol, ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture. Specific examples illustrating the preparation of unsubstituted piperazine-aryl-aldehydes are provided below.

The following step, the hydrazone formation is described above in general and below in detail.

Preparation of 4-piperazinyl-2,5-dimethylbenzaldehyde:

4-(2,5-dimethylphenyl)-1-benzylpiperazine:

A solution of 2,5-dimethylphenylpiperazine (20 g, 105 mmol) was prepared in acetonitrile (300 mL) and cooled to 0 °C. Benzyl bromide (19 g, 111 mmol) was added and the reaction mixture was stirred for 15 minutes before potassium carbonate (16 g, 116 mmol) was added. After stirring the mixture for two hours, the acetonitrile was evaporated and the residue taken up in water and ethyl acetate. The organic layer was separated and washed with brine and dried over magnesium sulfate. The benzylated product was purified by silica gel column chromatography using gradient hexane/ethyl acetate (10/0 to 8/2). The product (21 g, 71%) was obtained as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.24 (s, 3H), 2.29 (s, 3H), 2.60 (brd s, 4H), 2.92 (brd s, 4H), 3.55 (s, 2H), 6.78 (m, 1H), 6.84 (s, 1H), 7.04 (m, 1H), 7.30 (m, 5H).

4-(2,5-dimethyl-4-formylphenyl)-1-benzylpiperazine:

The 4-(2,5-dimethylphenyl)-1-benzylpiperazine (10 g, 36 mmol) was dissolved in anhydrous DMF (30 mL, 390 mmol) and cooled to 0 °C. Fresh POCl<sub>3</sub> (70 mL, 750 mmol) was added drop wise with stirring. Once the addition was completed the dark mixture was warmed to 75 °C for five hours or until TLC analysis indicated the disappearance of the starting materi-

al. The excess phosphorous oxychloride was distilled off and the entire mixture was diluted with ethyl acetate and added slowly to 500 mL of ice-chips. The solution was neutralized and made basic with concentrated NaOH. The neutralization and basification must be done at low temperatures to avoid creating by-products. The formylated product was extracted  
5 with ethyl acetate (5x). The organic layer was washed with water (2x), brine, dried over magnesium sulfate and purified by silica gel column chromatography using gradient hexane/ethyl acetate (10/0 to 8/2). The product (9 g, 81%) was obtained as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.29 (s, 3H), 2.28 (s + t, 7H), 3.03 (t, 4H), 3.59 (s, 2H), 6.75 (s, 1H), 7.31  
10 (m, 5H), 7.58 (s, 1H), 10.12 (s, 1H).

4-(2,5-dimethyl-4-formylphenyl)-1-(1-chloroethoxycarbonyl)piperazine:

The 4-(2,5-dimethyl-4-formylphenyl)-1-benzylpiperazine (9 g, 29 mmol) was dissolved in anhydrous 1,2-dichloroethane (100 mL) and 1-chloroethyl chloroformate (4.5 g, 31.5 mmol)  
15 was added. The solution was refluxed for 30 minutes or until TLC analysis indicated the disappearance of the starting material. The product was just slightly less polar than the starting material by TLC using hexane/EtOAc (3/1). Dichloroethane was evaporated and the residue was chromatographed using gradient hexane/EtOAc (10/0 to 8/2) to give the product (6 g, 64%) as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.84 (d, 3H), 2.32 (s, 3H), 2.61 (s, 3H), 2.99 (brd m, 4H), 3.70 (brd m, 4H), 6.62 (qt, 1H), 6.76 (s, 1H), 7.62 (s, 1H), 10.14 (s, 1H).

4-piperazinyl-2,5-dimethylbenzaldehyde:

To a solution of the dimethylphenylpiperazinylcarbamate above (6 g, 18.5 mmol) in THF (50 mL) was added 1 N HCl (50 mL, 50 mmol). The mixture was warmed to approximately 80  
25 °C until the evolution of CO<sub>2</sub> stopped. Most of the THF was removed by rotary evaporation and the residue was lyophilized to give the product as the dihydrochloride salt (5.5 g, 99%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 2.2 (s, 3H), 2.50 (s, 3H), 3.13 (brd s, 8H), 6.85 (s, 1H), 7.54 (s, 1H),  
30 9.49 (brd s, 2H), 10.02 (s, 1H).

4-piperazinyl-2,3-dimethylbenzaldehyde:

4-Piperazinyl-2,3-dimethylbenzaldehyde was prepared in the same fashion as above. For-  
5 mylation of the N-benzyl-piperazinyl-2,3-dimethylbenzene was much slower and required  
overnight heating at 70 °C. All other steps were otherwise very similar and the yields were  
comparable.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 2.15 (s, 3H), 2.47 (s, 3H), 3.07 (brd m, 4H), 3.17 (brd m, 4H), 5.90  
10 (brd s, 1H, NH), 7.02 (d, 1H), 7.50 (d, 1H), 9.54 (brd s, 2H, NH<sub>2</sub>), 10.10 (s, 1H).

4-piperazinyl-3,5-dimethylbenzaldehyde:

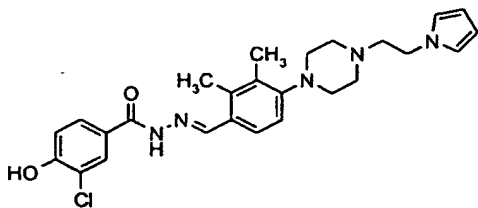
4-Piperazinyl-3,5-dimethylbenzaldehyde was prepared in the same manner as above.

General library procedure for N-alkylation and hydrazone formation:

To a solution of the unsubstituted piperazinyl-aryl-aldehyde in DMSO dispensed into 88 deep  
well plates were added solutions of desired alkylating agents (1 eq) in DMSO followed by  
20 diisopropylethylamine (5 eq). Solid potassium carbonate (5 eq) may also be substituted.  
After stirring the solutions for 16 hours, a solution of 4-hydroxybenzoic acid hydrazide deri-  
vative (1 eq) in DMSO and a solution of acetic acid (catalytic) in DMSO were added into e-  
ach well. The reaction mixtures were agitated for 16 hours to give the crude products which  
were purified by HPLC.

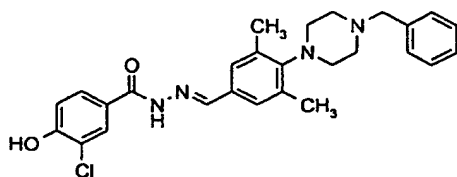
Examples of products:

EXAMPLE 521 :



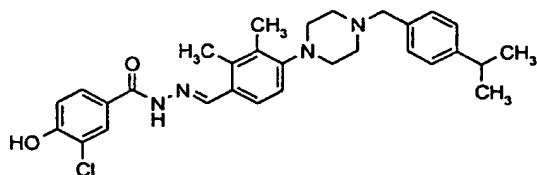
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.26 (s, 3H), 2.38 (s, 3H), 2.65 (brd s, 4H), 2.73 (t, 2H), 2.89 (brd s, 4H), 4.07 (t, 2H), 6.03 (d, 2H), 6.84 (t, 2H), 7.02 (d, 1H), 7.13 (d, 1H), 7.72 (d, 1H), 7.82 (dd, 1H), 8.01 (s, 1H), 8.86 (brd s, 1H), 11.68 (brd s, 1H); MS (APCI): 480.7, 482.3.

## EXAMPLE 522:



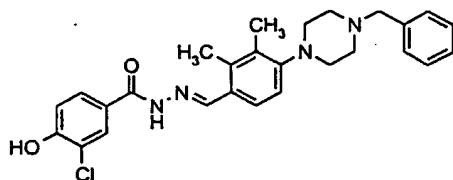
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.49 (s, 6H), 2.68 (brd s 4H), 3.22 (brd s, 4H), 3.72 (s, 2H), 7.22 (d, 1H), 7.44 (m, 1H), 7.52 (m, 6H), 7.92 (dd, 1H), 8.13 (s, 1H), 8.46 (s, 1H), 11.12 (brd s, 1H), 11.80 (s, 1H); MS (APCI): 477.5, 479.2.

## EXAMPLE 523:



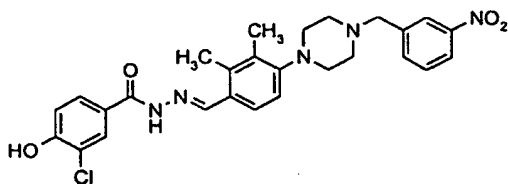
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.25 (s, 3H), 1.27 (s, 3H), 2.26 (s, 3H), 2.38 (s, 3H), 2.57 (brd s, 4H), 2.95 (brd s, 4H), 3.56 (s, 2H), 7.02 (d, 1H), 7.12 (d, 1H), 7.30 (qt, 4H), 7.72 (d, 1H), 7.82 (d, 1H), 8.01 (s, 1H), 8.83 (s, 1H), 11.0 (brd s, 1H), 11.1 (s, 1H); MS (APCI): 519.7, 521.5.

## EXAMPLE 524:



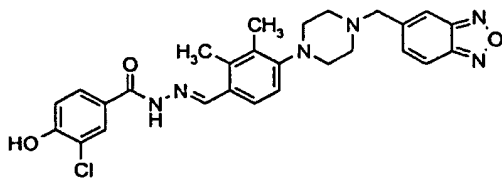
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.22 (s, 3H), 2.33 (s, 3H), 3.17 (brd s, 4H), 3.23 (m, 2H), 3.36 (m, 2H), 4.41 (s, 2H), 6.98 (d, 1H), 7.10 (d, 1H), 7.48 (m, 3H), 7.68 (m, 3H), 7.71 (d, 1H), 7.97 (s, 1H), 8.83 (s, 1H), 11.00 (s, 1H), 11.02 (brd s, 1H), 11.69 (s, 1H); MS (APCI): 477.4, 479.2.

## EXAMPLE 525:



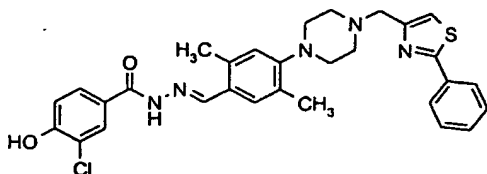
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.20 (s, 3H), 2.31 (s, 3H), 2.59 (s, 4H), 2.87 (s, 4H), 3.69 (s, 2H), 6.98 (d, 1H), 7.02 (d, 1H), 7.64 (m, 2H), 7.75 (dd, 1H), 7.82 (d, 1H), 7.94 (d, 1H), 8.12 (dd, 1H), 8.19 (s, 1H), 8.74 (s, 1H), 10.94 (brd s, 1H), 11.54 (s, 1H); MS (APCI): 522.2, 524.3.

## EXAMPLE 526:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.20 (s, 3H), 2.31 (s, 3H), 2.62 (brd s, 4H), 2.87 (brd s, 4H), 3.68 (s, 2H), 6.98 (d, 1H), 7.04 (d, 1H), 7.55 (d, 1H), 7.61 (d, 1H), 7.74 (dd, 1H), 7.91 (s, 1H), 7.92 (d, 1H), 8.01 (d, 1H), 8.74 (s, 1H), 10.93 (brd s, 1H), 11.54 (s, 1H); MS (APCI): 519.2, 521.3.

## EXAMPLE 527:

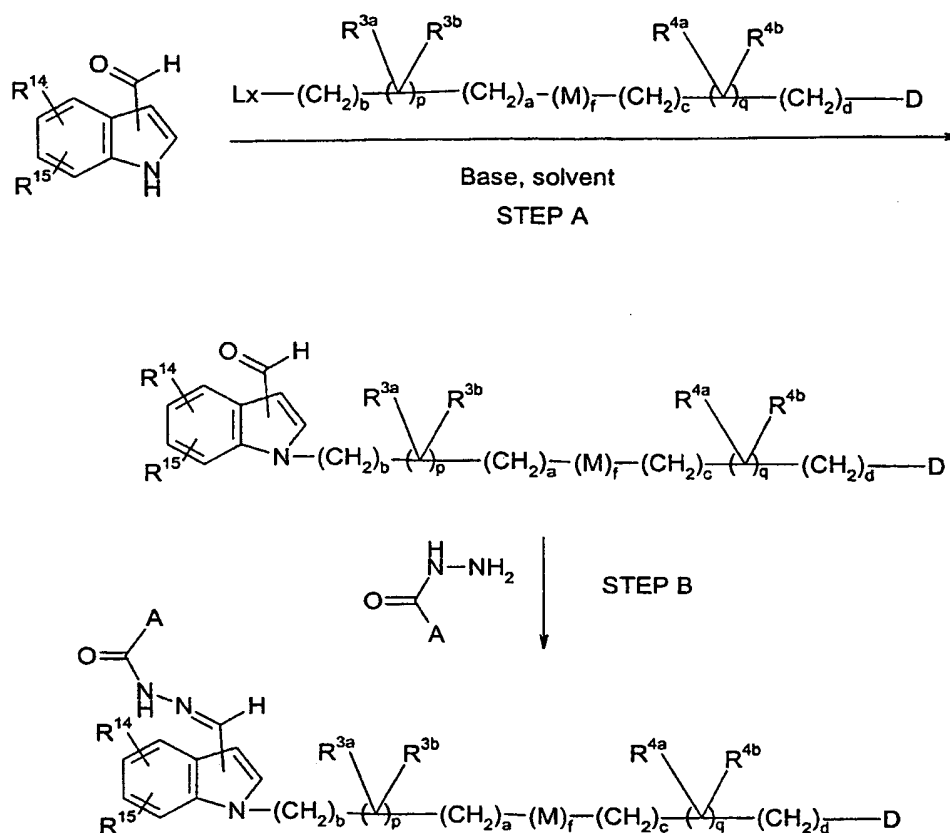


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 2.21 (s, 3H), 2.37 (s, 3H), 2.66 (brd s, 4H), 2.91 (brd s, 4H), 3.76 (s, 2H), 6.83 (s, 1H), 7.05 (d, 1H), 7.62 (s, 1H), 7.69 (s, 1H), 7.75 (dd, 1H), 7.86 (d, 2H), 7.94 (s, 1H), 8.15 (d, 2H), 8.60 (s, 1H), 10.92 (brd s, 1H), 11.55 (s, 1H); MS (APCI): 628.3, 630.2, 631.2.

General procedure for the synthesis of N-substituted indole aldehydes followed by hydrazo-  
ne formation:

10

The N-substituted indole aldehydes may be prepared by N-alkylation of the corresponding unsubstituted indole aldehydes using various electrophilic alkylating agents that introduce the - (K)<sub>m</sub>-D moiety as defined above.



wherein Lx is a leaving group such as -Cl, -Br, -I, -OSO<sub>2</sub>CH<sub>3</sub>, -OSO<sub>2</sub>p-tolyl or -OSO<sub>2</sub>CF<sub>3</sub>; and A, R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup>, a, b, c, d, f, p, q, D, M, R<sup>14</sup> and R<sup>15</sup> are as defined for formula I.

5

According to the above scheme the N-substituted indole aldehydes can be prepared by stirring formylindoles in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, DMSO, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, water or a compatible mixture of two or more of the above solvents with an equimolar amount of an alkyl halide or an aryl-lower alkyl halide and in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-collidine or benzyldimethylammonium methoxide or hydroxide. The reaction can be performed at 0°C to 150°C, preferably at 20°C to 100°C and

15

preferably in an inert atmosphere of N<sub>2</sub> or Ar. When the reaction is complete the mixture is filtered, concentrated in vacuo and the resulting product optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol, ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture.

The following step, the hydrazone formation is described above in general and below in detail.

**10 Library Procedure for Indole Alkylation (Step A):**

Preparation of the sodium salt of the indole:

Indole-3-carboxaldehyde (1.45 g) was dissolved into 8.6 mL of dry DMF in a dried and cooled 3 100 mL 3-necked roundbottom flask.

- 15 Evolution of large amounts of hydrogen gas occurs during this step. Care should be taken to keep the flow of inert gas steady and maintain adequate venting to accommodate the hydrogen gas evolution.

- 20 While maintaining a steady flow of nitrogen or argon through the 3-necked round bottomed flask, 1.1 equivalent of sodium hydride (0.27 g of dry 95% reagent) was transferred to the indole solution. The mixture was stirred for 15 minutes, while maintaining flow of inert gas. Proceeded promptly to the next step.

Preparation of the alkyl halide solutions:

- 25 Amber glass vials (for preparing stock solutions) were dried for at least four hours at 110 °C, then were allowed to cool under an argon atmosphere in a desiccator. Alkyl halides solutions (1.0 M) were prepared in anhydrous DMF in the dried vials. Each alkyl halide solution (100 µL) was added to its corresponding well of a deep-well plate (1 x 88 x 1 format).

Alkylation of the indole sodium salt:

100  $\mu$ L of the 1.0 M indole salt solution was quickly delivered to each alkyl halide in the deep-well plates. The plates were vortexed briefly to mix, then allowed to react for two hours.

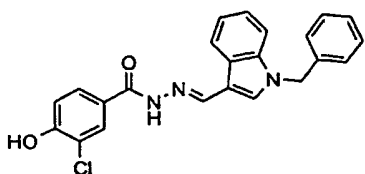
**5 Library Procedure for Hydrazone Formation (Step B):**Acyl Hydrazone formation:

3-Chloro-4-hydroxybenzoic acid hydrazide (1.86 g) was dissolved in 5 mL of dry DMSO, followed by trifluoroacetic acid (0.77mL). The resulting solution was diluted to a final volume of 10.0 mL. 100  $\mu$ L of the 1.0 M acid hydrazide TFA salt solution was added to each  
10 well of the deep-well plate. The plate was vortexed for one minute to mix, then allowed to react for 30 minutes.

The products were purified by chromatography on silica gel with ethyl acetate/hexane eluent.

15

The following compounds were prepared:

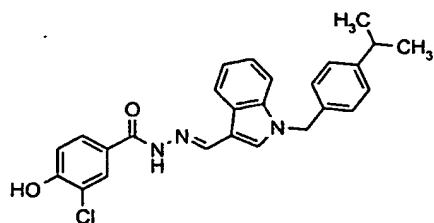
**EXAMPLE 528:**

20

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  5.46 (s, 2H), 7.10 (d,  $J$  = 8.7, 2H), 7.20 (m, 2H), 7.28 (m, 5H), 7.51 (d,  $J$  = 7.53, 1H), 7.79 (d,  $J$  = 7.9, 1H), 7.99 (s, 1H), 8.01 (s, 1H) 8.33 (d,  $J$  = 6.96, 1H), 8.62 (s, 1H), 10.9 (s, 1H), 11.5 (s, 1H); LRMS calcd for  $\text{C}_{26}\text{H}_{24}\text{Cl}_1\text{N}_3\text{O}_2$  (M - H) 402, found 402.1.

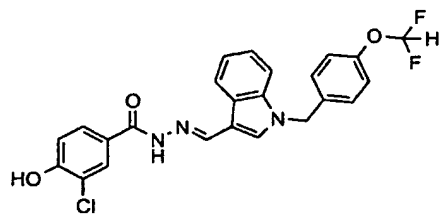
25

## EXAMPLE 529:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.14 (d, J = 6.8, 6H), 2.81 (sept, J = 6.9, 1H), 5.41 (s, 2H), 7.07 (d, J = 8.3, 1H), 7.20 (m, 6H), 7.54 (d, J = 7.6, 1H), 7.77 (d, J = 7.9, 1H), 7.97 (s, 1H), 8.01 (s, 1H), 8.29 (d, J = 7.2, 1H), 8.59 (s, 1H), 10.88 (s, 1H), 11.44 (s, 1H). LRMS calcd for C<sub>26</sub> H<sub>24</sub> Cl<sub>1</sub> N<sub>3</sub> O<sub>2</sub> (M - H) 445, found 445.9

## EXAMPLE 530:

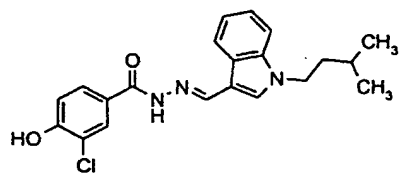


10

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 5.47 (s, 2H), 7.08 (d, J = 8.7, 1H), 7.13-7.25 (m, 5H), 7.18 (t, J = 74.2, 1H), 7.35 (d, J = 8.7, 1H), 7.54 (d, J = 7.9, 1H), 7.77 (dd, J = 8.7, 1.7, 1H), 7.97 (d, J = 1.7, 1H), 8.02 (s, 1H), 8.30 (d, J = 7.2, 1H), 8.59 (s, 1H), 10.89 (s, 1H), 11.45 (s, 1H). LRMS calcd for C<sub>24</sub> H<sub>18</sub> Cl<sub>1</sub> F<sub>2</sub> N<sub>3</sub> O<sub>3</sub> (M - H) 468, found 468.1.

15

## EXAMPLE 531:

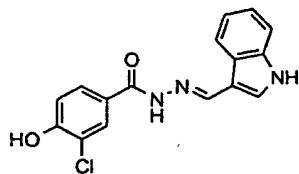


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 0.94 (d, J = 6.2, 6H), 1.54 (sept, J = 6.2, 1H), 1.66-1.73 (m, 2H), 4.23 (t, J = 7.0, 2H), 7.08 (d, J = 8.7, 1H), 7.16-7.29 (m, 2H), 7.54 (d, J = 7.95, 1H), 7.77 (d,

20

J = 8.7, 1H), 7.88 (s, 1H), 7.97 (s, 1H), 8.29 (d, J = 7.5, 1H), 8.57 (s, 1H), 10.88 (s, 1H). 11.42 (s, 1H). LRMS calcd for C<sub>21</sub> H<sub>22</sub> Cl, N<sub>3</sub> O<sub>2</sub> (M + H) 384, found 384.2.

EXAMPLE 532:

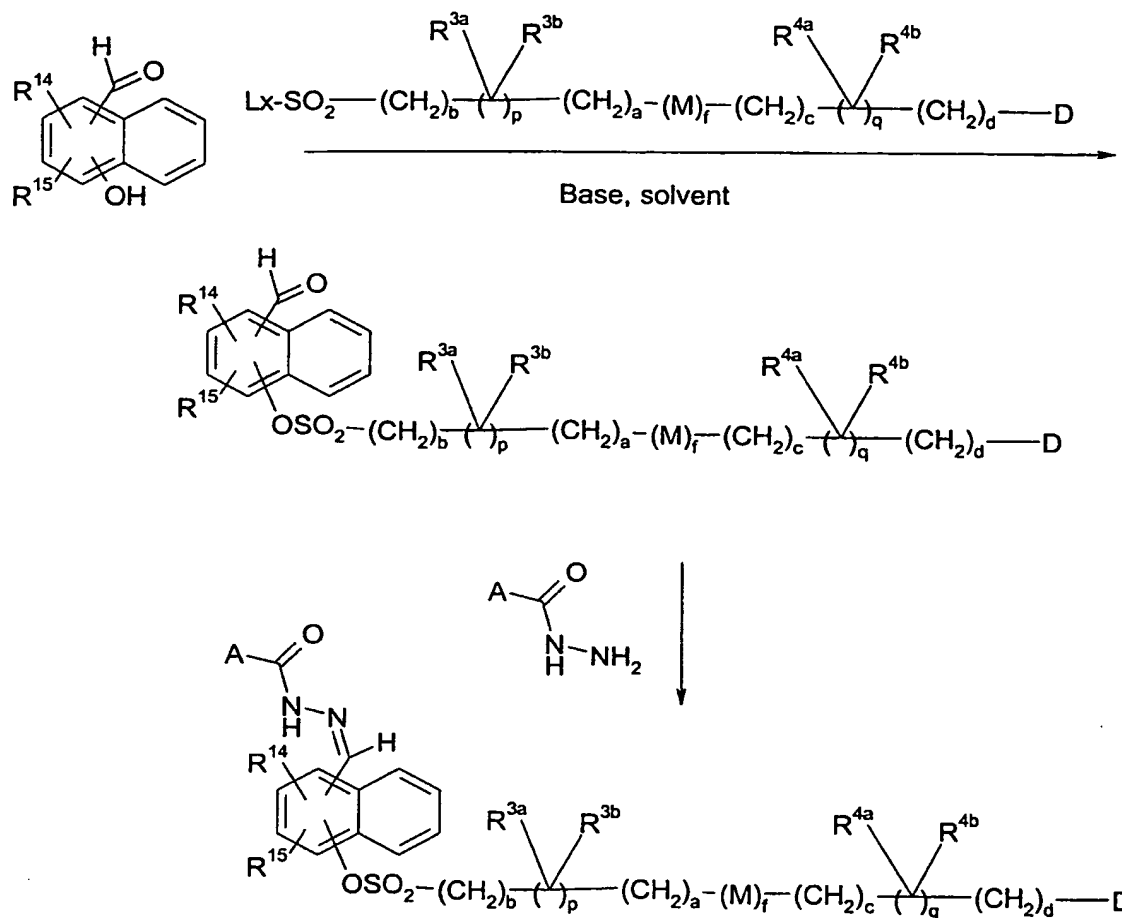


<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 7.06 (d, J = 8.5, 1H), 7.12-7.26 (m, 3H), 7.46-7.49 (m, 2H), 7.78 (d, J = 8.1, 1H), 7.99 (s, 1H), 11.33 (s, 1H), 11.65 (s, 1H). LRMS calcd for C<sub>16</sub> H<sub>12</sub> Cl, N<sub>3</sub> O<sub>2</sub> (M - H) 312, found 312.0.

10

General procedure for the synthesis of alkyl/aryl-sulfonyloxy aryl-aldehydes followed by hydrazone formation:

15 The alkyl/aryl-sulfonyloxy aryl-aldehydes may be prepared by O-sulfonylation of the corresponding phenolic compounds using various electrophilic sulfonylating agents that introduce the -(K)<sub>m</sub>-D moiety as defined above.



wherein Lx is a leaving group such as -Cl, -Br, -I, -OSO<sub>2</sub>CH<sub>3</sub>, -OSO<sub>2</sub>p-tolyl or -OSO<sub>2</sub>CF<sub>3</sub>; and A, R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup>, a, b, c, d, f, p, q, D, M, R<sup>14</sup> and R<sup>15</sup> are as defined for formula I.

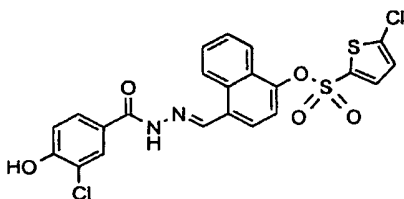
- 5 According to the above scheme an alkyl/aryl-sulfonyloxyaryl aldehyde can be prepared by stirring hydroxybenzaldehydes or hydroxynaphthaldehydes in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, water or a compatible mixture of two or more of the above solvents with an equimolar amount of an alkylsulfonylhalide, arylsulfonylhalide or an aryl-lower alkyl sulfonylhalide and in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-
- 10

collidine or benzyldimethyl- ammonium methoxide or hydroxide. The reaction can be performed at 0°C to 150°C, preferably at 20°C to 100°C and preferably in an inert atmosphere of N<sub>2</sub> or Ar. When the reaction is complete the mixture is filtered, concentrated *in vacuo* and the resulting product optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol, ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture.

The following hydrazone formation step is described above in general.

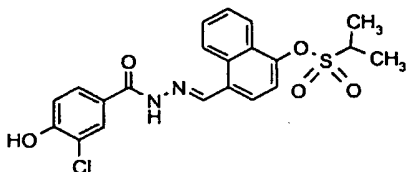
Examples of compounds synthesized using the methodology described are given below:

EXAMPLE 533:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 7.03 (d, 1H), 7.28 (d, 1H), 7.39 (d, 1H), 7.61 (t, 1H), 7.67 (t, 1H), 7.75 (m, 2H), 7.87 (d, 2H), 7.95 (s, 1H), 8.75 (d, 1H), 9.02 (s, 1H), 11.00 (s, 1H), 11.88 (s, 1H); MS (APCI): 521.0, 523.0.

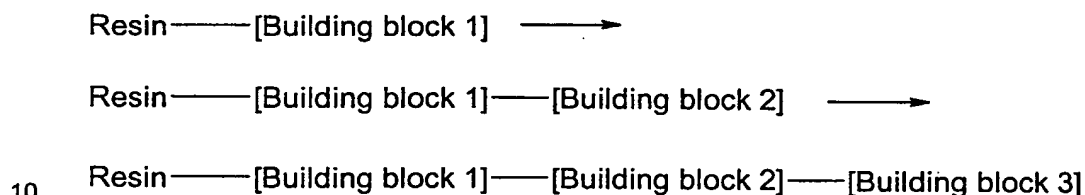
EXAMPLE 534:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.38 (d, 6H), 3.91 (septet, 1H), 6.97 (d, 1H), 7.46 (d, 1H), 7.61 (m, 2H), 7.71 (d, 1H), 7.81 (d, 1H), 7.89 (s, 1H), 8.01 (d, 1H), 8.69 (d, 1H), 9.11 (s, 1H), 11.00 (brd s, 1H), 11.98 (s, 1H); MS (APCI, neg.): 445.0, 487.0, 339 - iprso<sub>2</sub>.

5    General procedures for the preparation of alkylidene hydrazides according to the invention involving parallel synthesis on a solid support:

The compounds of Examples 535 to 614 were prepared according to the following equation



and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

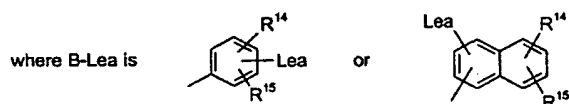
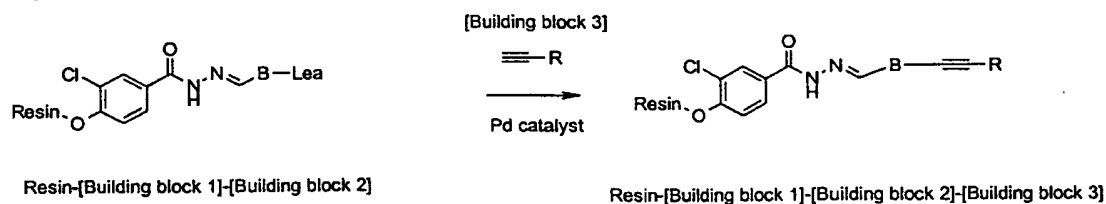


The following 80 compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1]-[Building block 2] was done manually,  
20    whereas the attachment of [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

The starting resins, Resin-[Building block 1]-[Building block 2], were all prepared as described below.

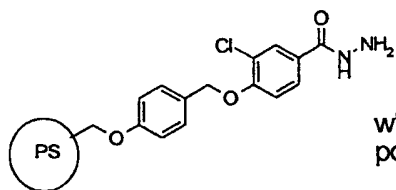
25    The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

All 80 compounds are based on attachment of [Building block 3] to Resin-[Building block 1]-[Building block 2] in a fully combinatorial way using a Heck reaction according to the following scheme:

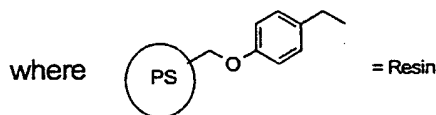


- 5 wherein Lea is a leaving group and preferably is selected from bromo, iodo and trifluoromethanesulfonyloxy, and R<sup>14</sup> and R<sup>15</sup> are as defined for formula I.

The following resin, here depicted as Resin-[Building block 1] was used:



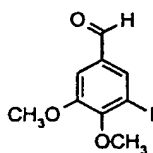
where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:



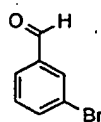
The following building blocks were used:

[Building block 2]:

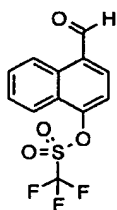
3,4-dimethoxy-5-iodobenzaldehyde



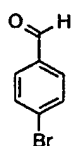
3-Bromobenzaldehyde



Trifluoromethanesulfonic acid 4-formyl-1-naphthyl ester

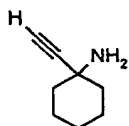


4-Bromobenzaldehyde

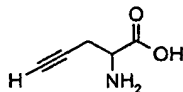


[Building block 3]:

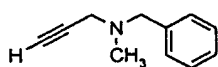
1-Ethynylcyclohexylamine



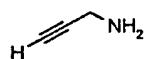
2-Amino-4-pentynoic acid



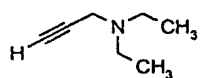
N-Methyl-N-propargylbenzylamine



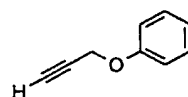
Propargylamine



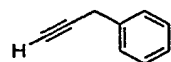
N,N-Diethylpropargylamine



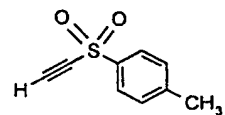
Phenyl propargyl ether



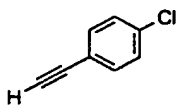
3-Phenyl-1-propyne



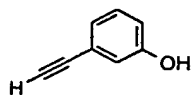
Ethynyl p-tolyl sulfone



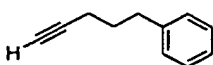
1-Chloro-4-ethynylbenzene



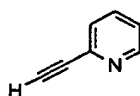
3-Ethynylphenol



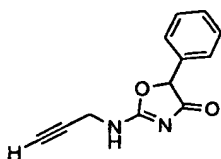
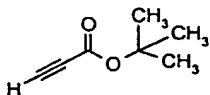
5-Phenyl-1-pentyne



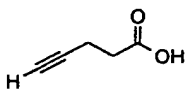
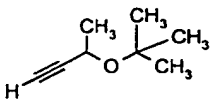
2-Ethynylpyridine



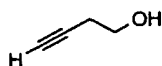
5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one

*tert*-Butyl propiolate

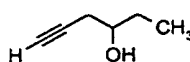
4-Pentynoic acid

*tert*-Butyl 1-methyl-2-propynyl ether

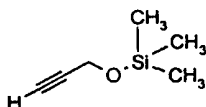
3-Butyn-1-ol



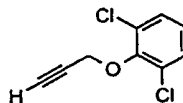
5-Hexyn-3-ol



O-Trimethylsilylpropargyl alcohol



3-(2,6-Dichlorophenoxy)prop-1-yne



By combination of these building blocks in a fully combinatorial way  $1 \times 4 \times 20 = 80$  compounds were prepared.

5

#### Preparation of [Building block 2]:

Preparation of 3,4-dimethoxy-5-iodobenzaldehyde:

Iodomethane (2.5 mL, 40 mmoles) was added to a mixture of 5-iodovanillin (10 g, 36 mmoles), potassium carbonate (25 g, 180 mmoles) in DMF (100 ml) and the resulting mixture was stirred at room temperature for 16 hours. The mixture was poured into water (0.5 L) and extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with water (200 mL), dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to afford 9.78 g (93%) of 3,4-dimethoxy-5-iodobenzaldehyde, m.p. 58-63 °C.

15

Preparation of trifluoromethanesulfonic acid 4-formyl-1-naphthyl ester:

4-Hydroxy-1-naphthaldehyde (10 g, 58 mmoles) was dissolved in pyridine (50 ml) and the mixture was cooled to 0 °C. Trifluoromethanesulfonic anhydride (11.7 mL, 70 mmoles) was added dropwise while maintaining the temperature below 5 °C. When the addition was completed the mixture was stirred at room temperature for 30 minutes. Diethyl ether (200 mL) was added and the mixture was successively washed with water (2 x 250 mL), 3 N hydrochloric acid (200 mL), and saturated NaCl (200 mL). The organic phase was dried over  $\text{MgSO}_4$  and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (800 mL) eluting with a mixture of ethyl acetate and heptane (1:4). Pure fractions

eluting with  $R_f = 0.46$  were pooled and evaporated *in vacuo* to afford 8.35 g (47 %) of trifluoromethanesulfonic acid 4-formyl-1-naphthyl ester, m.p. 44–47 °C.

The other [Building block 2]'s (3-Bromobenzaldehyde and 4-bromobenzaldehyde) are commercially available.

5

Preparation of Resin-[Building block 1]:

(Resin bound 3-chloro-4-hydroxybenzoic acid hydrazide)

Polystyrene resin (15 g) loaded with the Wang linker (0.92 mmoles/g), was successively washed with DMF (3 x 40 mL) and  $\text{CH}_2\text{Cl}_2$  (3 x 40 mL). The resin was suspended in  $\text{CH}_2\text{Cl}_2$  (80 mL) and diisopropylethylamine (60 mL) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (5.8 mL) dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added drop wise while maintaining the temperature below 5 °C. When addition was complete the mixture was stirred at 0 °C for 30 minutes and at room temperature for 30 minutes. The resin was successively washed with  $\text{CH}_2\text{Cl}_2$  (3 x 80 mL) and N-methylpyrrolidone (NMP) (3 x 80 mL). This resin and cesium carbonate (12.3 g) were added to ethyl 3-chloro-4-hydroxybenzoate (15 g) dissolved in NMP (200 mL) and the mixture was stirred at 80 °C for 4 hours. After cooling the resin was successively washed with NMP (3 x 80 mL) and methanol (3 x 80 mL).

The above resin was suspended in 1,4-dioxane (150 mL) and water (36 mL). Lithium hydroxide (2.6 g) was added and the mixture was stirred at 60 °C under  $\text{N}_2$  for 16 hours. After cooling the resin was successively washed with DMF (3 x 80 mL),  $\text{CH}_2\text{Cl}_2$  (3 x 80 mL) and methanol (80 mL) and dried *in vacuo* at 50 °C for 3 days.

The above resin (3.0 g) was suspended in  $\text{CH}_2\text{Cl}_2$  (20 mL) and 1-hydroxybenzotriazole (0.6 g), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, hydrochloride (0.9 g) and DMF (10 mL) were added. The mixture was shaken at room temperature for 45 minutes, hydrazine hydrate (300  $\mu\text{L}$ ) was added, and the mixture was shaken overnight at room temperature. The resin was successively washed with DMF (3 x 20 mL) and  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL) to afford resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (Resin-[Building block 1]).

30

Preparation of Resin-[Building block 1]-[Building block 2]:

Preparation of resin bound 3-chloro-4-hydroxybenzoic acid (3,4-dimethoxy-5-iodobenzylidene)hydrazide:

The above resin (Resin-[Building block 1]) (4 g) was suspended in DMF (50 mL) and 3,4-dimethoxy-5-iodobenzaldehyde (5.8 g) and triethyl orthoformate (25 mL) were added and the mixture was shaken for 16 hours at room temperature. The resin was successively washed with DMF (4 x 40 mL) and CH<sub>2</sub>Cl<sub>2</sub> (6 x 40 mL), and dried in vacuo at 50 °C  
5 for 16 hours to afford resin bound 3-chloro-4-hydroxybenzoic acid (3,4-dimethoxy-5-iodobenzylidene)hydrazide.

Preparation of resin bound trifluoromethanesulfonic acid 4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]naphthalen-1-yl ester:

10 Similarly as described above but using trifluoromethanesulfonic acid 4-formyl-1-naphthyl ester instead of 3,4-dimethoxy-5-iodobenzaldehyde resin bound was trifluoromethanesulfonic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]naphthalen-1-yl ester obtained.

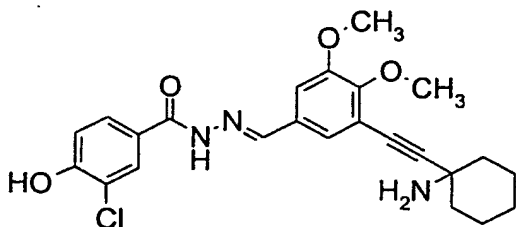
Preparation of resin bound 3-chloro-4-hydroxybenzoic acid (3-bromobenzylidene)hydrazide:

15 Similarly as described above but using 3-bromobenzaldehyde instead of 3,4-dimethoxy-5-iodobenzaldehyde resin bound 3-chloro-4-hydroxybenzoic acid (3-bromobenzylidene)hydrazide) was obtained.

Preparation of resin bound 3-chloro-4-hydroxybenzoic acid (4-bromobenzylidene)hydrazide:

20 Similarly as described above but using 4-bromobenzaldehyde instead of 3,4-dimethoxy-5-iodobenzaldehyde resin bound 3-chloro-4-hydroxybenzoic acid (4-bromobenzylidene)-hydrazide) was obtained.

## EXAMPLE 535:



3-Chloro-4-hydroxybenzoic acid [3-(1-aminocyclohexylethynyl)-4,5-dimethoxybenzylidene]-hydrazide

5

To the resin bound 3-chloro-4-hydroxybenzoic acid (3-bromobenzylidene)hydrazide (0.05 mmols) was added copper (I) iodide (10 mg). Diisopropylethylamine (0.2 mL), a solution of triphenylphosphine in NMP (0.4 M, 0.5 mL), a solution of tetrabutylammonium chloride in water (0.66 M, 0.3 mL), a solution of palladium (II) acetate in NMP (0.16 M, 0.25 mL) and a  
10 solution of 1-ethynylcyclohexylamine ([Building block 3]) in NMP (1 M, 0.5 mL) were added successively, and the mixture was shaken at 90 °C for 15 hours. The resin was repeatedly washed with NMP (1.5 mL, 3 times), 50% water in DMF (1.5 mL, 3 times), NMP (1.5 mL, 2 times), 1% sodium diethylaminodithiocarbamate trihydrate (1.5 mL, 9 times), NMP (1.5 mL, 5 times), and CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 6 times) for 2 minutes and filtered.

15

The compound was cleaved off the resin by shaking for 45 minutes at room temperature with a 50% solution of trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). The mixture was filtered and the resin was extracted with CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and  
20 concentrated in vacuo to give the title compound.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

25 The RP-HPLC analysis was performed on a Waters HPLC system consisting of Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5 μ C-18 Symmetry column and Millenium

QuickSet Control Ver. 2.15 using UV detection at 214 nm. A gradient of 5% to 90% acetonitrile/0.1% trifluoroacetic acid/water during 15 minutes at 1 mL/minute.

- The LC-MS analysis was performed on a PE Sciex API 100 LC/MS System using a Waters™
- 5 3 mm x 150 mm 3.5  $\mu$  C-18 Symmetry column and positive ionspray with a flow rate at 20  $\mu$ L/minute.

Examples 536 to 614:

- A library of the following 79 compounds can be prepared in parallel as individual entities analogously to example 535 on an Advanced ChemTech Model 384 HTS using the following
- 10 ChemFile to control the operation of the synthesizer. The 4 resins of type Resin-[Building block 1]-[Building block 2] are equally distributed in the 80 wells in the synthesizer prior to the initialization of the device.

ChemFile C:\ACT\90250004.CHM Page 1

- 15 1 Empty RB\_Heating\_All\_1to36 for 2.000 minute(s)  
2 REM Addition of DIPEA  
3 Transfer 200 $\mu$ l from Monomers\_1to36 [25] ( ) to RB\_Heating\_All\_1to96 [1-80] using DCE  
4 Mix for 1.00 minutes at 600 rpm(s)  
5 REM Addition of Ph3P in NMP
- 20 6 Transfer 500 $\mu$ l from Monomers\_1to36 [21] ( ) to RB Heating\_All\_1to96 [1-80] using DCE  
7 REM Addition of Bu4NCl in water  
8 Transfer 300 $\mu$ l from Monomers\_1to36 [22] ( ) to RB Heating\_All\_1to96 [1-80] using DCE  
9 Mix for 1.00 minutes at 600 rpm(s)  
10 REM Addition of Pd(OAc)2 in NMP
- 25 11 Transfer 250 $\mu$ l from Monomers\_1to36 [22] ( ) to RB\_Heating\_All\_1to96 [1-80] using DCE  
12 Mix for 2.00 minutes at 600 rpm(s)  
13 Dispense Sequence C:\ACT\ALKYNES.DSP with 500 $\mu$ l to RB\_Heating\_All\_1to96 rack  
14 Set Temperature to 90.0 degrees Celsius  
15 Mix for 15.00 minutes at 600 rpm(s)
- 30 16 Wait for 15.000 minute(s)  
17 Repeat from step 15, 47 times  
18 Turn Temperature Controller Off  
19 Mix for 15.00 minutes at 600 rpm(s)  
20 Wait for 15.000 minute(s)
- 35 21 Repeat from step 19, 7 times  
22 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
23 Dispense System Fluid NMP1 1500 $\mu$ l to RB\_Cleavage\_All\_1to96 [1-80]  
24 Mix for 3.00 minutes at 600 rpm(s)  
25 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 40 26 Repeat from step 23, 2 times  
27 REM Wash with 50% H2O/NMP

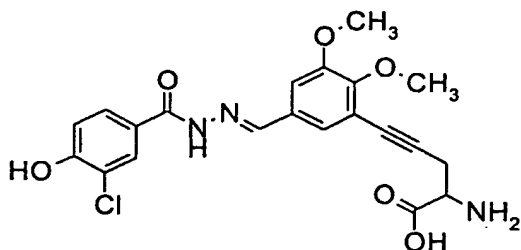
- 28 Transfer 1500µl from Reagent\_3 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1  
29 Mix for 3.00 minutes at 600 rpm(s)  
30 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
31 Repeat from step 28, 2 times  
5 32 Dispense System Fluid NMP1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]  
33 Mix for 3.00 minutes at 600 rpm(s)  
34 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
35 Repeat from step 32, 1 times  
36 REM Wash with Sodium diethylaminodithiocarbamate  
10 37 Transfer 1500µl from Reagent\_3 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1  
38 Mix for 3.00 minutes at 600 rpm(s)  
39 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
40 Repeat from step 37, 2 times  
41 Transfer 1500µl from REAGENT\_4 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1  
15 42 Mix for 3.00 minutes at 600 rpm(s)  
43 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
44 Repeat from step 41, 2 times  
45 Transfer 1500µl from REAGENT\_5 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1  
46 Mix for 2.00 minutes at 600 rpm(s)  
20 47 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
48 Repeat from step 45, 2 times  
49 Dispense System Fluid NMP1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]  
50 Mix for 3.00 minutes at 600 rpm(s)  
51 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
25 52 Repeat from step 49, 4 times  
53 Dispense System Fluid DCE1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]  
54 Mix for 3.00 minutes at 600 rpm(s)  
55 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
56 Repeat from step 53, 5 times  
30 57 REM Cleavage from Resin  
58 REM with 50% TFA/DCM  
59 Transfer 1500µl from Reagent\_3 [1] ( ) to RB\_Cleavage\_All\_1to96 [1-80] using DCM1  
60 Mix for 45.00 minutes at 600 rpm(s)  
61 Empty RB\_Cleavage\_All\_1to96 for 1.000 minute(s)  
35 62 Dispense System Fluid DCM1 500µl to RB\_Cleavage\_All\_1to96 [1-80]  
63 Mix for 1.00 minutes at 300 rpm(s)  
64 Empty RB\_Cleavage\_All\_1to96 for 1.000 minute(s)  
65  
66  
40

Dispense Sequence C:\ACTALKYNES.DSP is a subroutine that controls the combinatorial addition of the solutions of the 20 alkynes of type [Building block 3] into the 80 wells in the synthesizer.

The library containing the compounds listed below was synthesized. A subset of the library obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

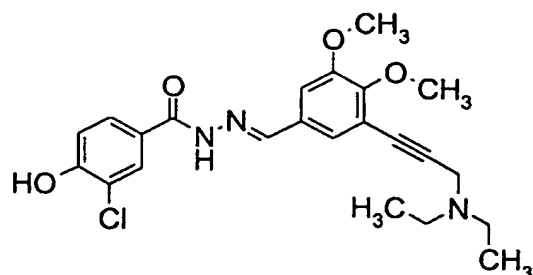
## EXAMPLE 536:

2-Amino-5-{5-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentynoic acid



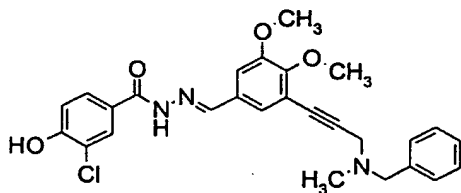
## EXAMPLE 537:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propynyl)-4,5-dimethoxybenzylidene]hydrazide



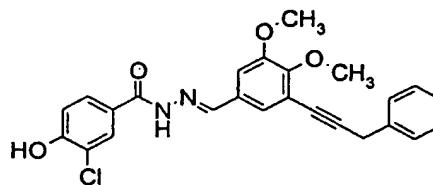
## EXAMPLE 538:

3-Chloro-4-hydroxybenzoic acid [3-[3-(benzylmethylamino)-1-propynyl]-4,5-dimethoxybenzylidene]hydrazide



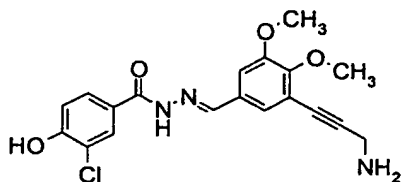
## EXAMPLE 539:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenyl-1-propynyl)benzylidene]hydrazide



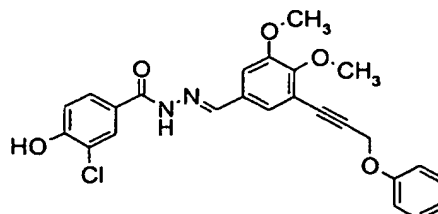
## EXAMPLE 540:

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propynyl)-4,5-dimethoxybenzylidene]hydrazide



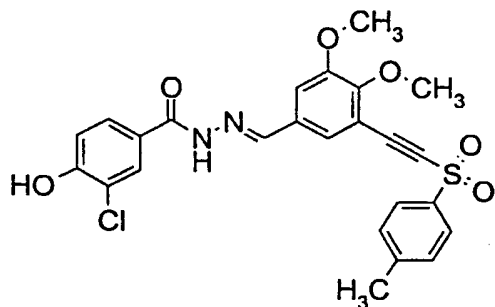
## EXAMPLE 541:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenoxy-1-propynyl)benzylidene]hydrazide



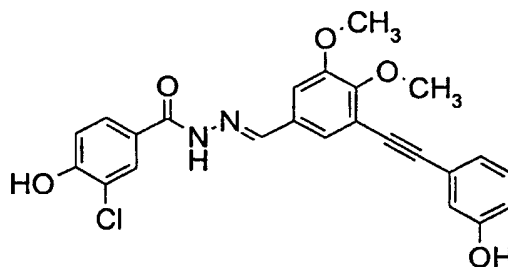
## EXAMPLE 542:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(toluene-4-sulfonylethynyl)-benzylidene]hydrazide



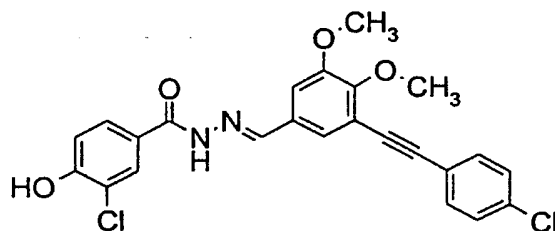
## EXAMPLE 543:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxyphenylethynyl)-4,5-dimethoxybenzylidene]hydrazide



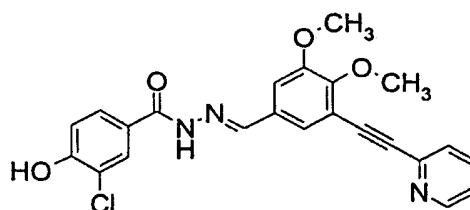
## EXAMPLE 544:

3-Chloro-4-hydroxybenzoic acid [3-(4-chlorophenylethynyl)-4,5-dimethoxybenzylidene]hydrazide



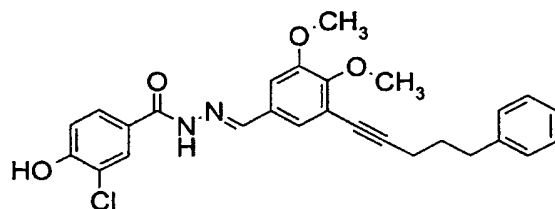
## EXAMPLE 545:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(2-pyridylethynyl)-benzylidene]hydrazide



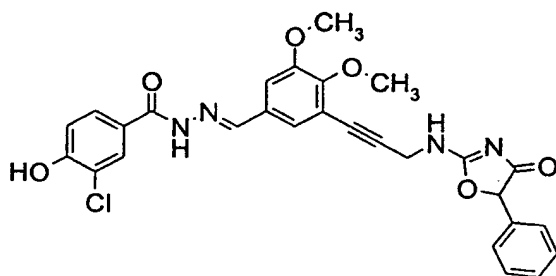
## EXAMPLE 546:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(5-phenyl-1-pentynyl)benzylidene]hydrazide



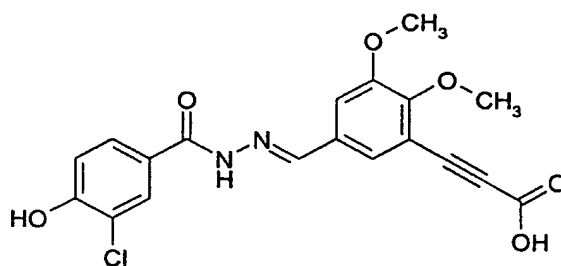
## EXAMPLE 547:

3-Chloro-4-hydroxybenzoic acid {3,4-dimethoxy-5-[3-(4-oxo-5-phenyl-4,5-dihydro-2-oxazolylamino)-1-propynyl]-benzylidene}hydrazide



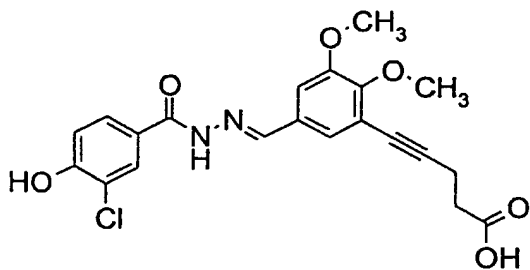
## EXAMPLE 548:

{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxy-phenyl}propynoic acid



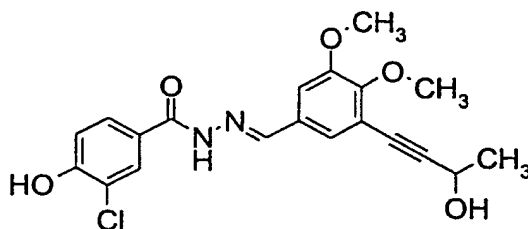
## EXAMPLE 549:

5-{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentynoic acid



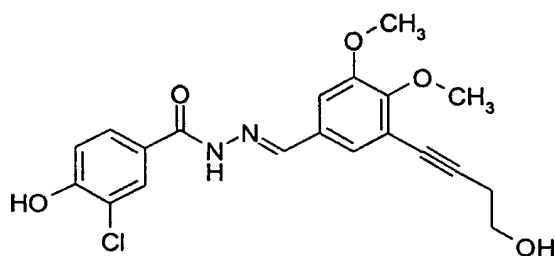
## EXAMPLE 550:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-butyryl)-4,5-dimethoxybenzylidene]hydrazide



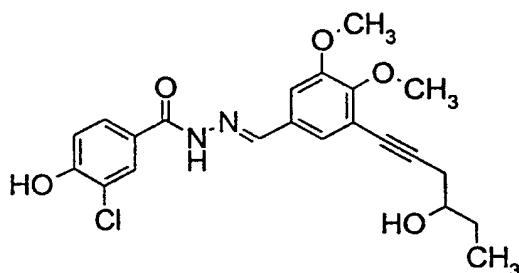
## EXAMPLE 551:

3-Chloro-4-hydroxybenzoic acid [3-(4-hydroxy-1-butynyl)-4,5-dimethoxybenzylidene]hydrazide



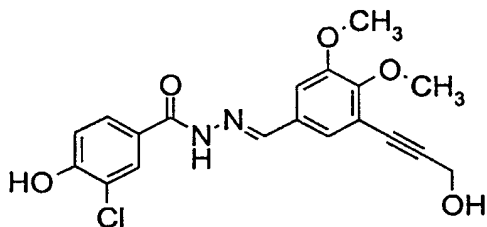
## EXAMPLE 552:

3-Chloro-4-hydroxybenzoic acid [3-(4-hydroxy-1-hexynyl)-4,5-dimethoxybenzylidene]hydrazide



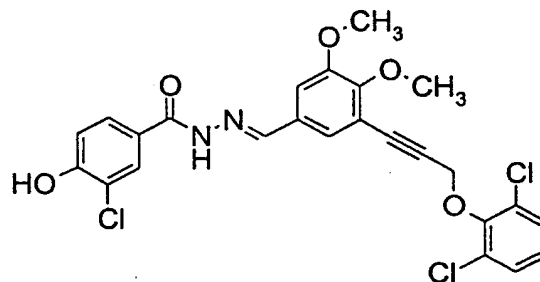
## EXAMPLE 553:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-propynyl)-4,5-dimethoxybenzylidene]hydrazide



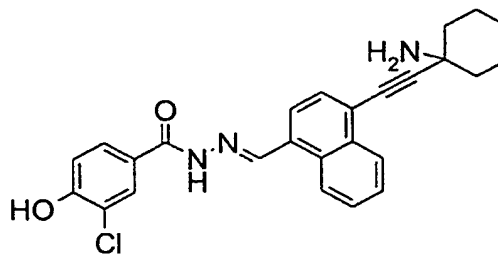
## EXAMPLE 554:

3-Chloro-4-hydroxybenzoic acid {3-[3-(2,6-dichlorophenoxy)-1-propynyl]-4,5-dimethoxybenzylidene}hydrazide



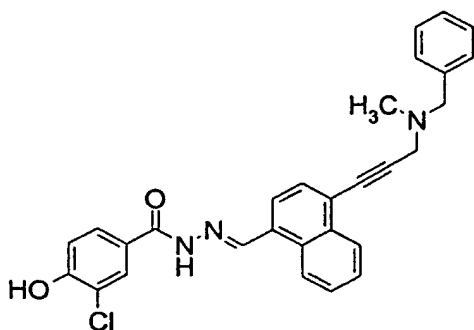
## EXAMPLE 555:

3-Chloro-4-hydroxybenzoic acid [4-(1-aminocyclohexylethynyl)-1-naphthylmethylene]hydrazide



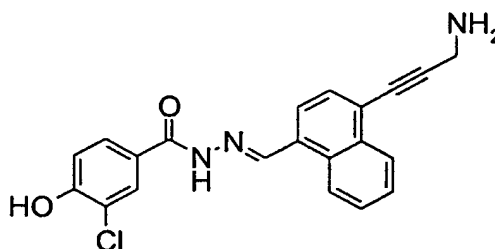
## EXAMPLE 556:

3-Chloro-4-hydroxy benzoic acid [4-(3-benzylmethylamino-1-propynyl)-1-naphthylmethylene] hydrazide



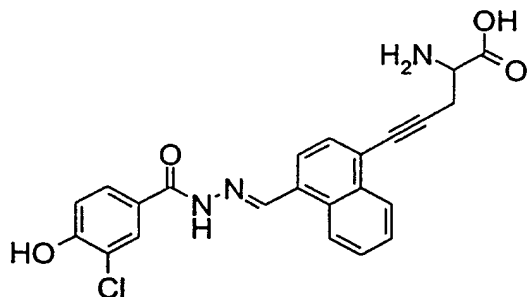
## EXAMPLE 557:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propynyl)-1-naphthylmethylene]hydrazide



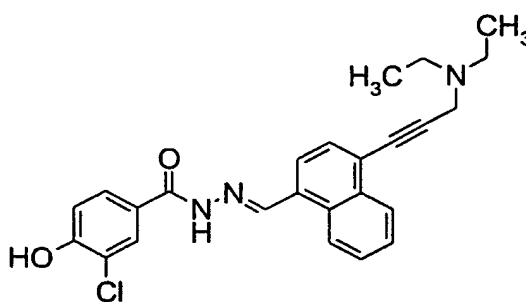
## EXAMPLE 558:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentynoic acid



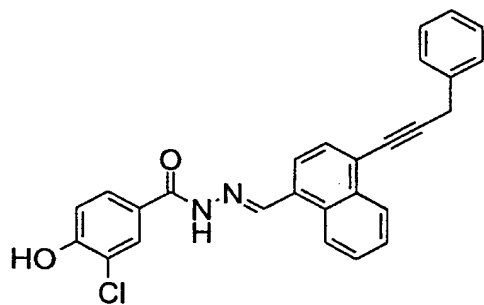
## EXAMPLE 559:

3-Chloro-4-hydroxybenzoic acid[4-(3-diethylamino-1-propynyl)-1-naphthylmethylene]hydrazide



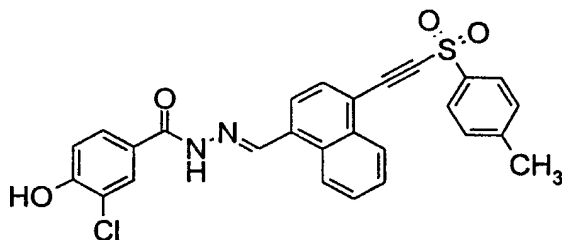
## EXAMPLE 560:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenyl-1-propynyl)-1-naphthylmethylene]hydrazide



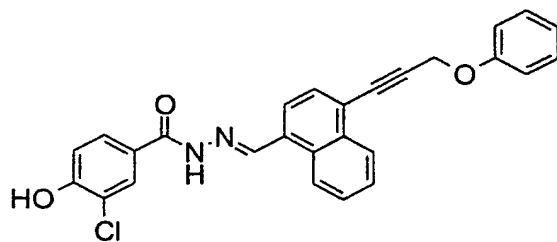
## EXAMPLE 561:

3-Chloro-4-hydroxybenzoic acid [4-(toluene-4-sulfonyl-1-propynyl)-1-naphthylmethylene]hydrazide



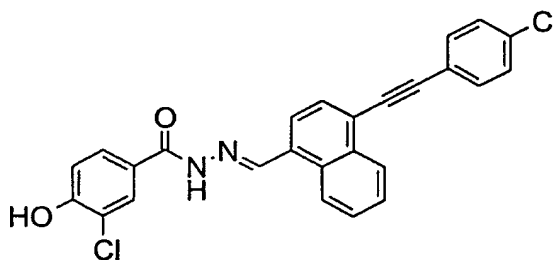
## EXAMPLE 562:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenoxy-1-propynyl)-1-naphthylmethylene]hydrazide



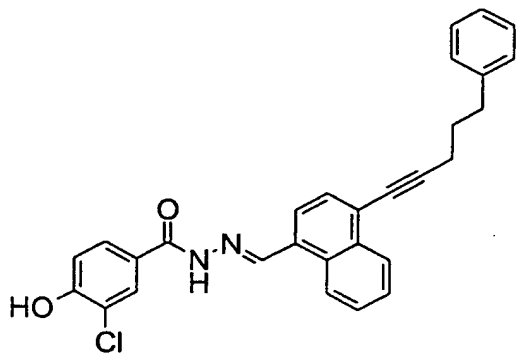
## EXAMPLE 563:

3-Chloro-4-hydroxybenzoic acid [4-(4-chlorophenyl-1-propynyl)-1-naphthylmethylene]hydrazide



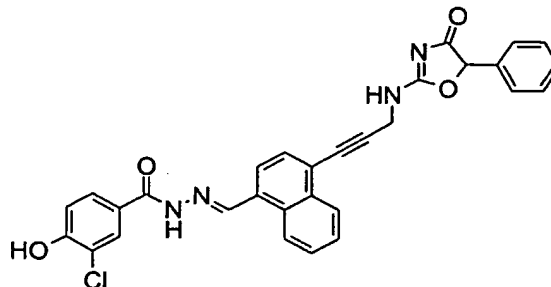
## EXAMPLE 564:

3-Chloro-4-hydroxybenzoic acid [4-(5-phenyl-1-pentynyl)-1-naphthylmethylene]hydrazide



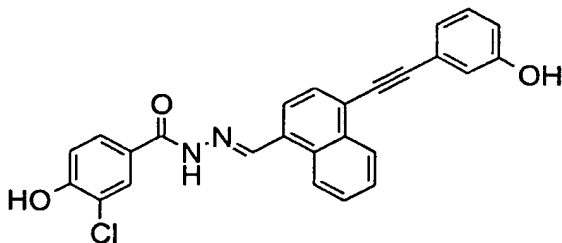
## EXAMPLE 565:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propynyl)-1-naphthylmethylene]hydrazide



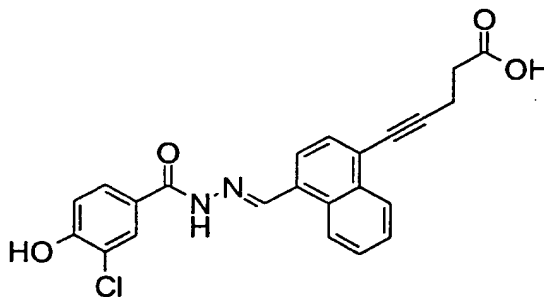
## EXAMPLE 566:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxyphenylethynyl)-1-naphthylmethylene]hydrazide



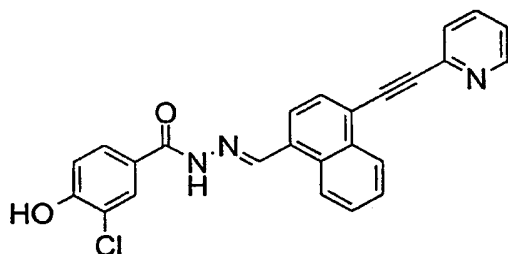
## EXAMPLE 567:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentoic acid



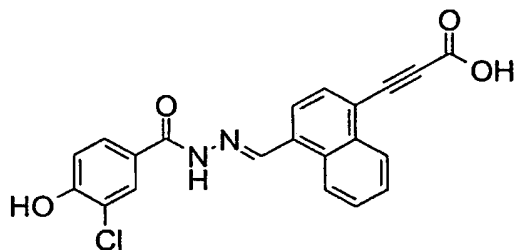
## EXAMPLE 568:

3-Chloro-4-hydroxybenzoic acid [4-(2-pyridyl)ethynyl-1-naphthylmethylene]-hydrazide



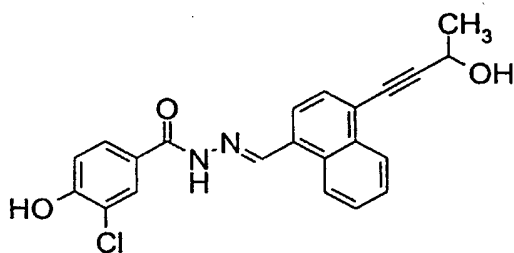
## EXAMPLE 569:

{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}propynoic acid



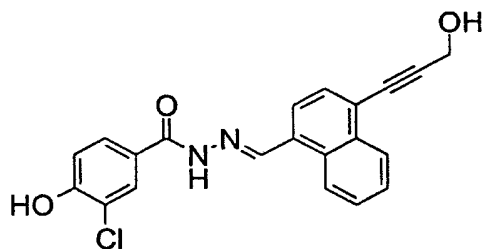
## EXAMPLE 570:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-butynyl)-1-naphthylmethylene]-hydrazide



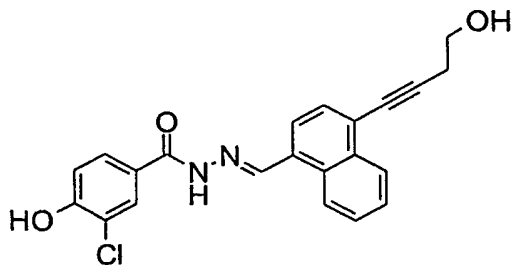
## EXAMPLE 571:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-propynyl)-1-naphthylmethylene]-hydrazide



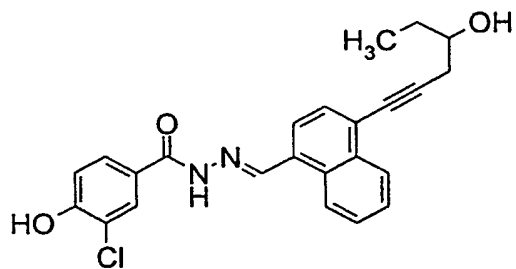
## EXAMPLE 572:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-butynyl)-1-naphthylmethylene]-hydrazide



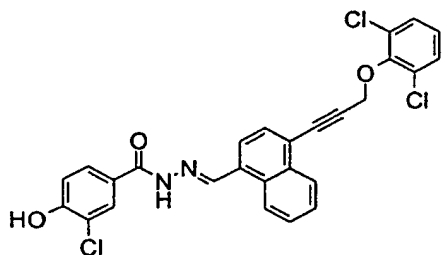
## EXAMPLE 573:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-hexynyl)-1-naphthylmethylene]-hydrazide



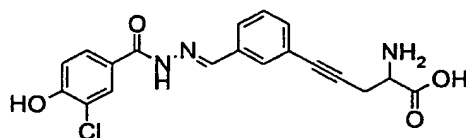
## EXAMPLE 574:

3-Chloro-4-hydroxybenzoic acid {4-[3-(2,6-dichlorophenoxy)-1-propynyl]-1-naphthylmethylene}hydrazide



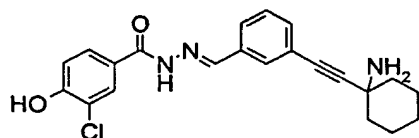
## EXAMPLE 575:

2-Amino-5-{3-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]phenyl}-4-pentynoic acid



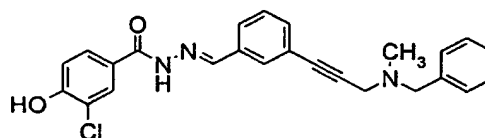
## EXAMPLE 576:

3-Chloro-4-hydroxybenzoic acid [3-(1-aminocyclohexylethynyl)benzylidene]hydrazide



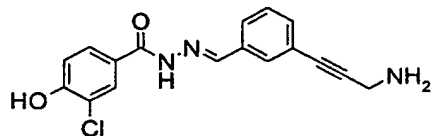
## EXAMPLE 577:

3-Chloro-4-hydroxybenzoic acid {3-[3-(benzylmethylamino)-1-propynyl]benzylidene}hydrazide



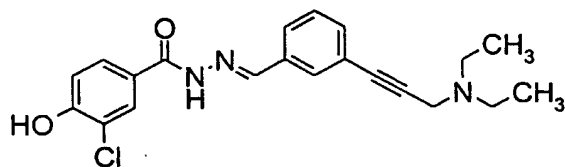
## EXAMPLE 578:

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propynyl)benzylidene]hydrazide



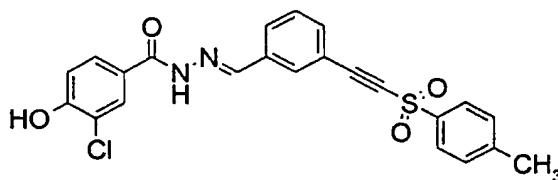
## EXAMPLE 579:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propynyl)benzylidene]hydrazide



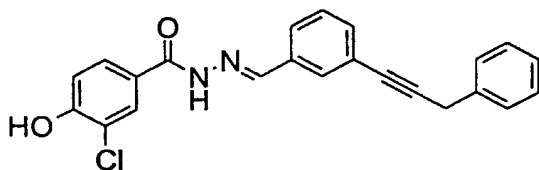
## EXAMPLE 580:

3-Chloro-4-hydroxybenzoic acid [3-(toluene-4-sulfonylethynyl)benzylidene]hydrazide



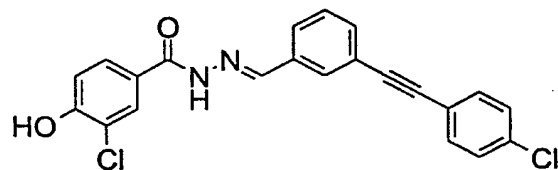
## EXAMPLE 581:

3-Chloro-4-hydroxybenzoic acid [3-(3-phenyl-1-propynyl)benzylidene]hydrazide



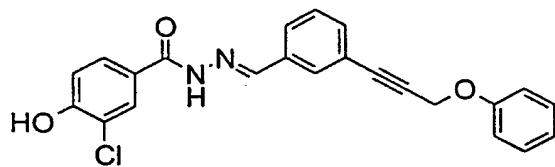
## EXAMPLE 582:

3-Chloro-4-hydroxybenzoic acid [3-(4-chlorophenylethynyl)benzylidene]hydrazide



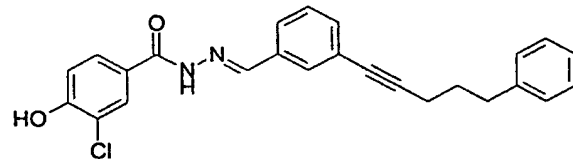
## EXAMPLE 583:

3-Chloro-4-hydroxybenzoic acid [3-(3-phenoxy-1-propynyl)benzylidene]hydrazide



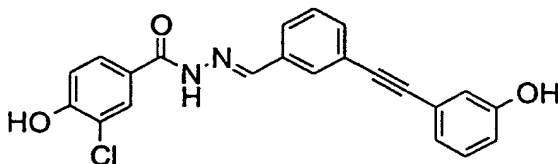
## EXAMPLE 584:

3-Chloro-4-hydroxybenzoic acid [3-(5-phenyl-1-pentynyl)benzylidene]hydrazide



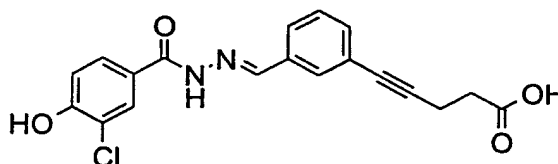
## EXAMPLE 585:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxyphenylethynyl)benzylidene]-hydrazide



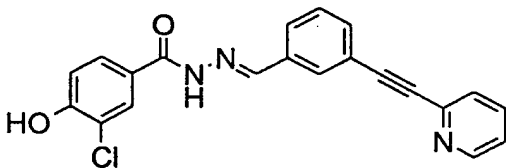
## EXAMPLE 586:

5-{3-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentynoic acid



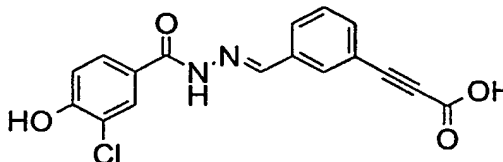
## EXAMPLE 587:

3-Chloro-4-hydroxybenzoic acid [3-(2-pyridylethynyl)benzylidene]hydrazide



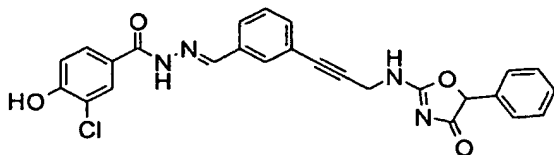
## EXAMPLE 588:

{3-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}propynoic acid



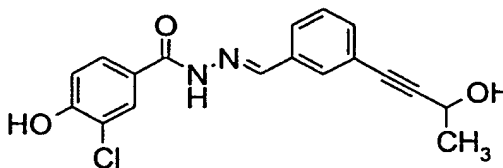
## EXAMPLE 589:

3-Chloro-4-hydroxybenzoic acid {3-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino))-1-propynyl]benzylidene}hydrazide



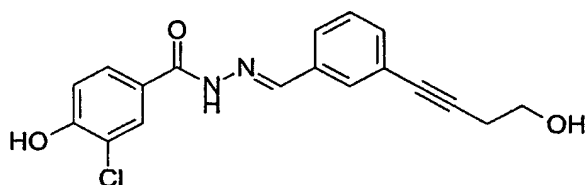
## EXAMPLE 590:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-butynyl)benzylidene]hydrazide



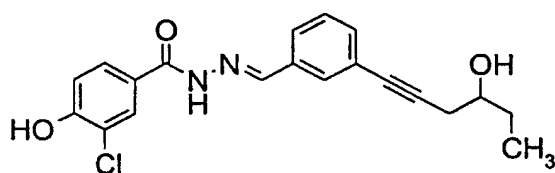
## EXAMPLE 591:

3-Chloro-4-hydroxybenzoic acid [3-(4-hydroxy-1-butynyl)benzylidene]hydrazide



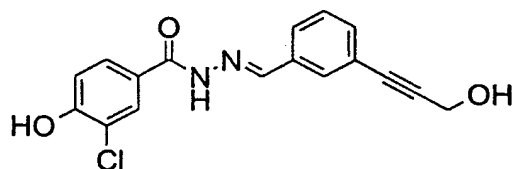
## EXAMPLE 592:

3-Chloro-4-hydroxybenzoic acid [3-(4-hydroxy-1-hexynyl)benzylidene]hydrazide



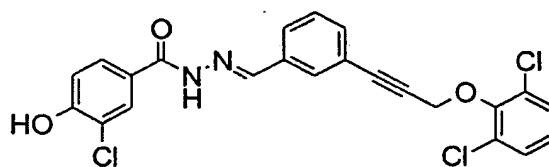
## EXAMPLE 593:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-propynyl)benzylidene]hydrazide



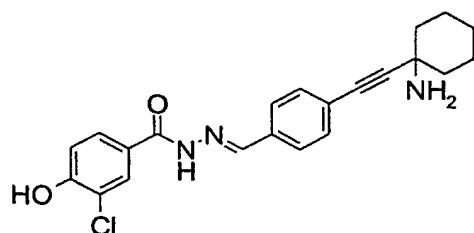
## EXAMPLE 594:

3-Chloro-4-hydroxybenzoic acid {3-[3-(2,6-dichlorophenoxy)-1-propynyl]benzylidene}hydrazide



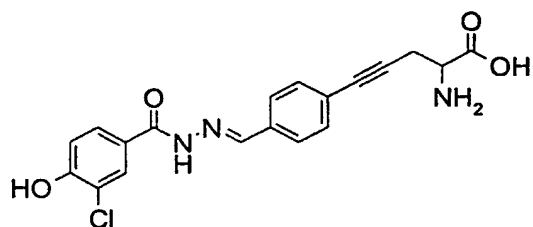
## EXAMPLE 595:

3-Chloro-4-hydroxybenzoic acid [4-(1-aminocyclohexylethynyl)benzylidene]hydrazide



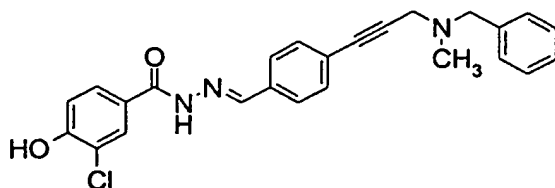
## EXAMPLE 596:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentynoic acid



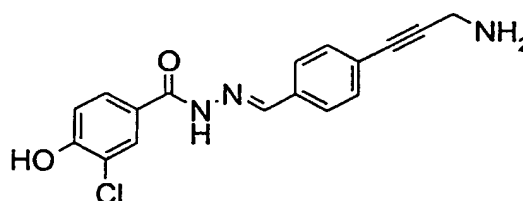
## EXAMPLE 597:

3-Chloro-4-hydroxybenzoic acid {4-[3-(benzylmethylamino)-1-propynyl]-benzylidene}hydrazide



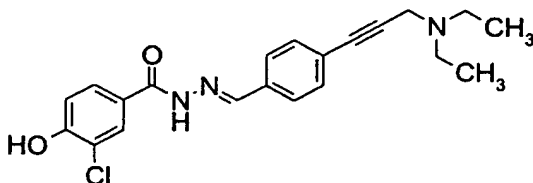
## EXAMPLE 598:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propynyl)benzylidene]hydrazide



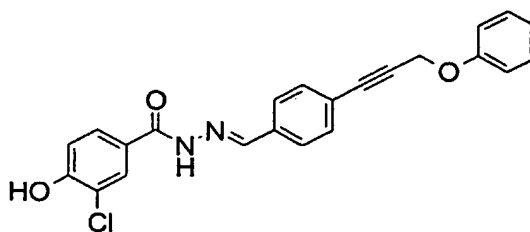
## EXAMPLE 599:

3-Chloro-4-hydroxybenzoic acid [4-(3-diethylamino-1-propynyl)benzylidene]-hydrazide



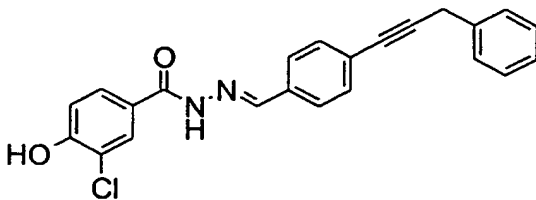
## EXAMPLE 600:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenoxy-1-propynyl)benzylidene]hydrazide



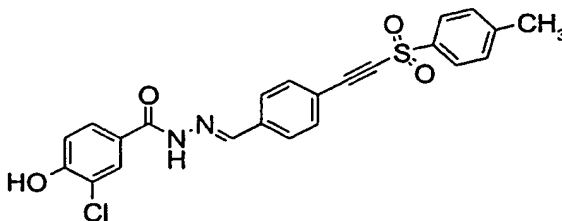
## EXAMPLE 601:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenyl-1-propynyl)benzylidene]hydrazide



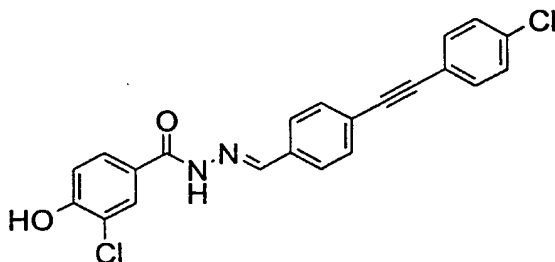
## EXAMPLE 602:

3-Chloro-4-hydroxybenzoic acid [4-(toluene-4-sulfonylpropynyl)benzylidene]hydrazide



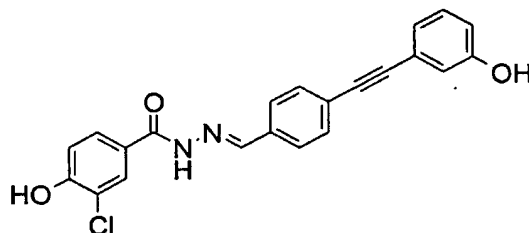
## EXAMPLE 603:

3-Chloro-4-hydroxybenzoic acid [4-(4-chlorophenylethynyl)benzylidene]hydrazide



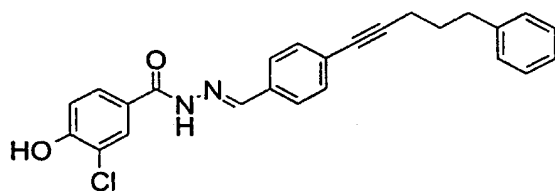
## EXAMPLE 604:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxyphenylethynyl)benzylidene]hydrazide



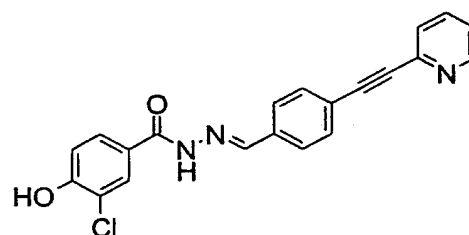
## EXAMPLE 605:

3-Chloro-4-hydroxybenzoic acid [4-(5-phenyl-1-pentynyl)benzylidene]hydrazide



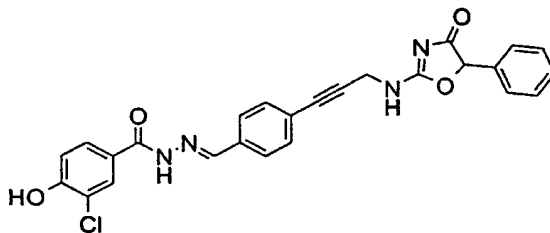
## EXAMPLE 606:

3-Chloro-4-hydroxybenzoic acid [4-(2-pyridylethynyl)benzylidene]hydrazide



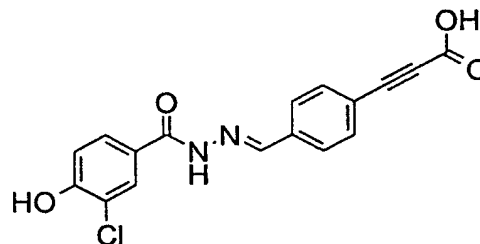
## EXAMPLE 607:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propynyl)benzylidene]hydrazide



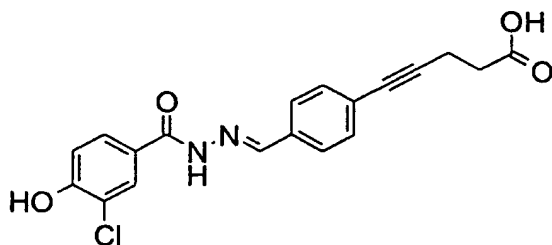
## EXAMPLE 608:

{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-phenyl}propynoic acid



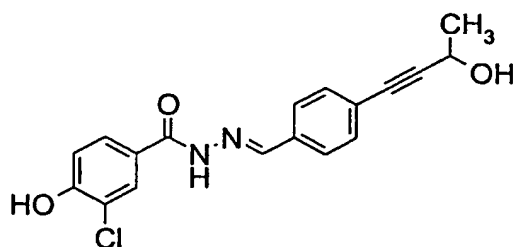
## EXAMPLE 609:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-  
hydrazonomethyl]phenyl}-4-pentynoic acid



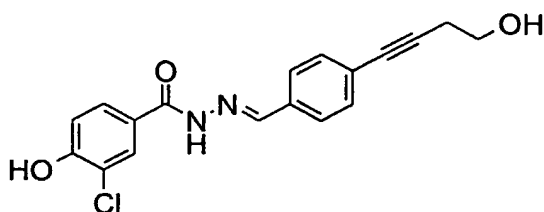
## EXAMPLE 610:

3-Chloro-4-hydroxybenzoic acid [4-(3-  
hydroxy-1-butynyl)benzylidene]hydrazide



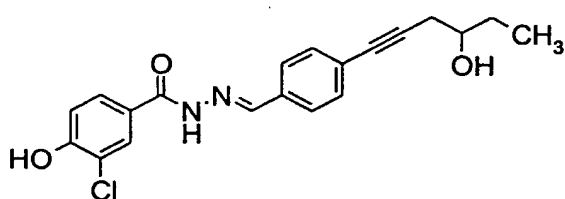
## EXAMPLE 611:

3-Chloro-4-hydroxybenzoic acid [4-(4-  
hydroxy-1-butynyl)benzylidene]hydrazide



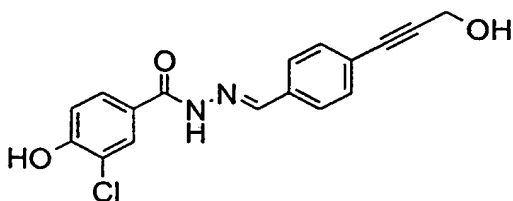
## EXAMPLE 612:

3-Chloro-4-hydroxybenzoic acid [4-(4-  
hydroxy-1-hexynyl)benzylidene]hydrazide



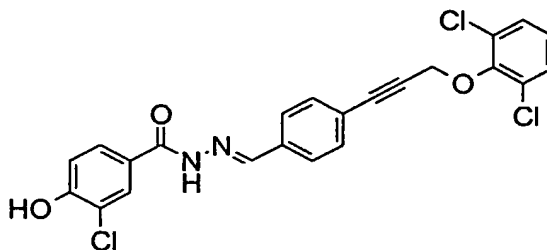
## EXAMPLE 613:

3-Chloro-4-hydroxybenzoic acid [4-(3-  
hydroxy-1-propynyl)benzylidene]hydrazide



## EXAMPLE 614:

3-Chloro-4-hydroxybenzoic acid {4-[3-(2,6-  
dichlorophenoxy)-1-propynyl]benzylidene}-  
hydrazide

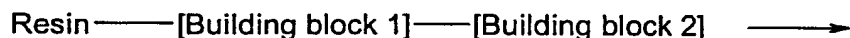


General procedure for the preparation of Examples 615 to 694:

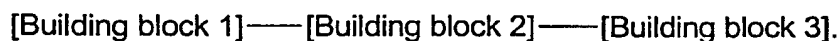
The following 80 compounds were prepared as single entities by parallel synthesis on a solid support. The attachment of [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

5

The compounds were prepared according to the following equation:



- 10 and were simultaneously cleaved (and deprotected when protected) from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula:

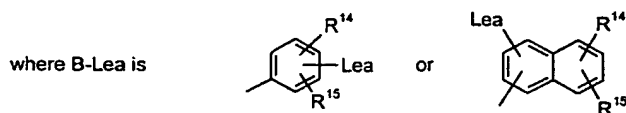
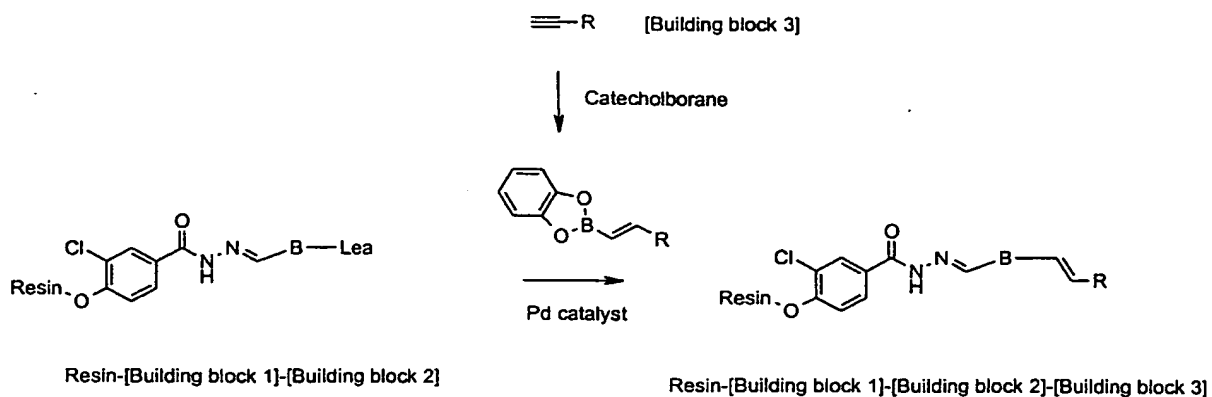


15

The starting resins, Resin-[Building block 1]-[Building block 2], were all prepared as described above.

- 20 The resin used was a polystyrene resin loaded with a Wang linker and the substitution capacity was 0.9 mmol/g.

All 80 compounds are based on attachment of [Building block 3] to Resin-[Building block 1]-[Building block 2] in a fully combinatorial way using a Suzuki reaction according to the following scheme.



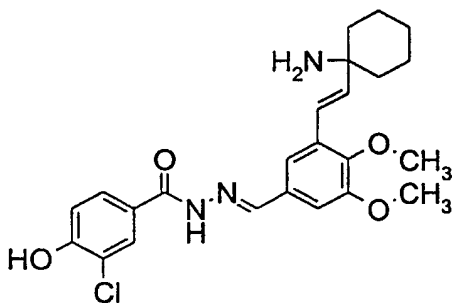
wherein Lea is a leaving group and  $R^{14}$  and  $R^{15}$  are as defined for formula I.

The starting materials used were the same as those use in examples 535 to 614, i.e.

- 5 Resin-[Building block 1], [Building block 2] and [Building block 3] were the same as those used in examples 535 to 614, the only difference being the products in examples 615 to 694 are having double bonds as compared to the products in examples 535 to 614 having triple bonds.

## EXAMPLE 615:

3-Chloro-4-hydroxybenzoic acid {3-[2-(1-aminocyclohexyl)vinyl]-4,5-dimethoxybenzylidene}-hydrazide



5

Preparation of a 1,4-dioxane/THF solution of 1-(2-Benzo[1,3,2]dioxaborol-2-ylvinyl)cyclohexylamine:

To a solution of 1-ethynylcyclohexylamine ([Building block 3]) in 1,4-dioxane (1 M, 0.5 mL) was added a solution of catecholborane in THF (1 M, 0.5 mL) and the mixture was heated at 60 °C for 4 hours. The solution was cooled to room temperature and used directly in the Suzuki coupling reaction.

To the resin bound 3-chloro-4-hydroxybenzoic acid (3-bromobenzylidene)hydrazide (0.05 mmoles) was added a solution of cesium carbonate in water (1.25 M, 0.2 mL), a solution of triphenylphosphine and tetrabutylammonium chloride in NMP (both 0.4 M, 0.5 mL), a solution of palladium (II) acetate in NMP (0.16 M, 0.25 mL), was mixed and the solution of 1-(2-benzo[1,3,2]dioxaborol-2-ylvinyl)cyclohexylamine in 1,4-dioxane/THF (prepared as described above) was added and the mixture was shaken at 70 °C for 15 hours. The resin was repeatedly washed with NMP (1.5 mL, 3 times), 50% water in DMF (1.5 mL, 3 times), NMP (1.5 mL, 2 times), 1% sodium diethylaminodithiocarbamate trihydrate (1.5 mL, 9 times), NMP (1.5 mL, 5 times) and CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 6 times) for 2 minutes and filtered.

The compound was cleaved off the resin by shaking for 45 minutes at room temperature with a 50% solution of trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). The mixture was filtered and the resin was extracted with CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were concentrated

in vacuo. The residue was dissolved in a 1:1 mixture of methanol and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and concentrated in vacuo to give the title compound.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by  
5 LC-MS (molecular mass).

The RP-HPLC analysis was performed on a Waters HPLC system consisting of Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5 μ C-18 Symmetry column and Millennium  
10 QuickSet Control Ver. 2.15 using UV detection at 214 nm. A gradient of 5% to 90% acetonitrile/0.1% trifluoroacetic acid/water at 15 minutes at 1 mL/minute.

The LC-MS analysis was performed on a PE Sciex API 100 LC/MS System using a Waters™ 3 mm x 150 mm 3.5 μ C-18 Symmetry column and positive ionspray with a flow rate at 20  
15 μL/minute.

#### EXAMPLES 616 to 694:

A library of the following 79 compounds can be prepared in parallel as individual entities analogously to example 615 on an Advanced ChemTech Model 496 HTS using the following ChemFile to control the operation of the synthesizer. The 4 resins of type Resin-[Building  
20 block 1]-[Building block 2] are equally distributed in the 80 wells in the synthesizer prior to the initialization of device.

ChemFile C:\ACT\90250003.CHM Page 1

1 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)  
25 2  
3 REM Addition of Cs<sub>2</sub>CO<sub>3</sub> in water  
4  
5 Transfer 200μl from Monomers\_1to36 [25] ( ) to RB\_Heating\_All\_1to96 [1-80] using DCE  
6 Mix for 1.00 minutes at 600 rpm(s)  
30 7  
8 REM Addition of Ph<sub>3</sub>P + Bu<sub>4</sub>NCl in NMP  
9  
10 Transfer 500μl from Monomers\_1to36 [21] ( ) to RB\_Heating\_All\_1to96 [1-80] using DCE  
11 Mix for 1.00 minutes at 600 rpm(s)  
35 12  
13 REM Addition of Pd(OAc)<sub>2</sub> in NMP  
14  
15 Transfer 500μl from Monomers\_1to36 [22] ( ) to RB\_Heating\_All\_1to96 [1-80] using DCE

- 16 Mix for 2.00 minutes at 600 rpm(s)
- 17 Dispense Sequence C:\ACTALKYNES.DSP with 500µl to RB\_Heating\_All\_1to96 rack
- 18 Set Temperature to 70.0 degrees Celsius
- 19 Mix for 15.00 minutes at 600 rpm(s)
- 5 20 Wait for 15.000 minute(s)
- 21 Repeat from step 19, 29 times
- 22 Turn Temperature Controller Off
- 23 Mix for 15.00 minutes at 600 rpm(s)
- 24 Wait for 15.000 minute(s)
- 10 25 Repeat from step 23, 7 times
- 26 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 27 Dispense System Fluid NMP1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]
- 28 Mix for 3.00 minutes at 600 rpm(s)
- 29 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 15 30 Repeat from step 27, 2 times
- 31
- 32 REM Wash with 50% H2O/NMP
- 33
- 34 Transfer 1500µl from Reagent\_3 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1
- 20 35 Mix for 3.00 minutes at 600 rpm(s)
- 36 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 37 Repeat from step 34, 2 times
- 38 Dispense System Fluid NMP1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]
- 39 Mix for 3.00 minutes at 600 rpm(s)
- 25 40 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 41 Repeat from step 38, 1 times
- 42
- 43 REM Wash with Sodium diethylaminodithiocarbamate
- 44
- 30 45 Transfer 1500µl from Reagent\_3 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1
- 46 Mix for 3.00 minutes at 600 rpm(s)
- 47 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 48 Repeat from step 45, 2 times
- 49 Transfer 1500µl from REAGENT\_4 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1
- 35 50 Mix for 3.00 minutes at 600 rpm(s)
- 51 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 52 Repeat from step 49, 2 times
- 53 Transfer 1500µl from REAGENT\_5 [1] ( ) to RB\_Heating\_All\_1to96 [1-80] using NMP1
- 54 Mix for 2.00 minutes at 600 rpm(s)
- 40 55 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 56 Repeat from step 53, 2 times
- 57 Dispense System Fluid NMP1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]
- 58 Mix for 3.00 minutes at 600 rpm(s)
- 59 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 45 60 Repeat from step 57, 4 times
- 61 Dispense System Fluid DCE1 1500µl to RB\_Cleavage\_All\_1to96 [1-80]
- 62 Mix for 3.00 minutes at 600 rpm(s)
- 63 Empty RB\_Heating\_All\_1to96 for 2.000 minute(s)
- 64 Repeat from step 61, 5 times

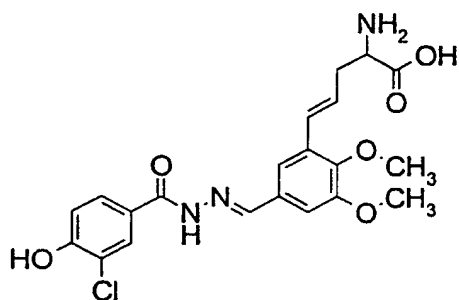
- 65
- 66 REM Cleavage from Resin
- 67 REM with 50% TFA/DCM
- 68
- 5 69 Transfer 1500µl from Reagent\_3 [1] ( ) to RB\_Cleavage\_All\_1to96 [1-80] using DCM1
- 70 Mix for 45.00 minutes at 600 rpm(s)
- 71 Empty RB\_Cleavage\_All\_1to96 for 1.000 minute(s)
- 72 Dispense System Fluid DCM1 500µl to RB\_Cleavage\_All\_1to96 [1-80]
- 73 Mix for 1.00 minutes at 300 rpm(s)
- 10 74 Empty RB\_Cleavage\_All\_1to96 for 1.000 minute(s)
- 75

- Dispense Sequence C:\ACTALKYNES.DSP is a subroutine that controls the combinatorial addition of the solutions of the 20 2-vinyl-benzo[1,3,2]dioxaboroles of type [Building block 3]
- 15 into the 80 wells in the synthesizer.

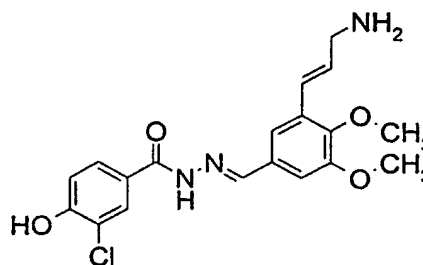
The library containing the compounds listed below was synthesized. A subset of the library obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

**EXAMPLE 616:**

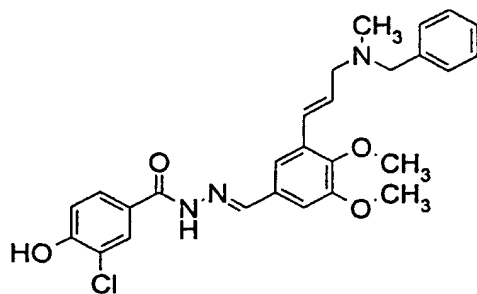
2-Amino-5-{5-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentenoic acid

**EXAMPLE 617:**

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propenyl)-4,5-dimethoxybenzylidene]hydrazide

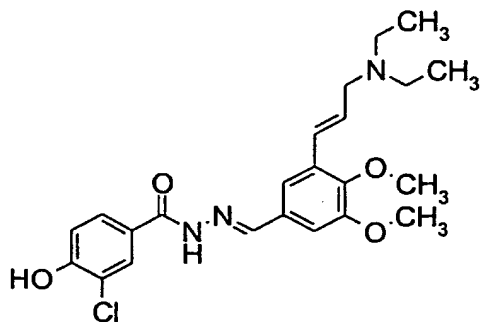
**EXAMPLE 618:**

3-Chloro-4-hydroxybenzoic acid {3-[3-(benzylmethylamino)propenyl]-4,5-dimethoxybenzylidene}hydrazide



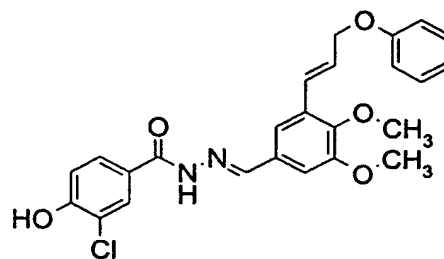
## EXAMPLE 619:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propenyl)-4,5-dimethoxybenzylidene]hydrazide



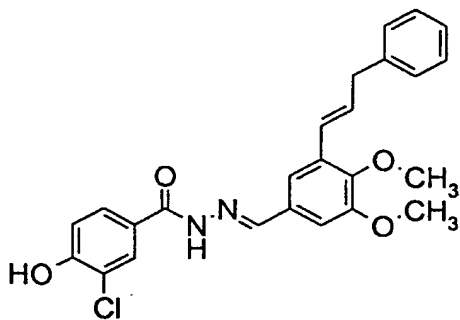
## EXAMPLE 620:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenoxy-1-propenyl)-benzylidene]hydrazide



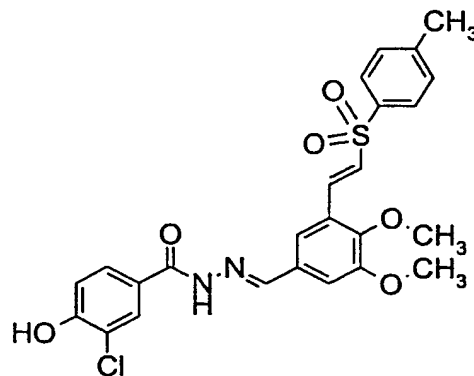
## EXAMPLE 621:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenyl-1-propenyl)-benzylidene]hydrazide



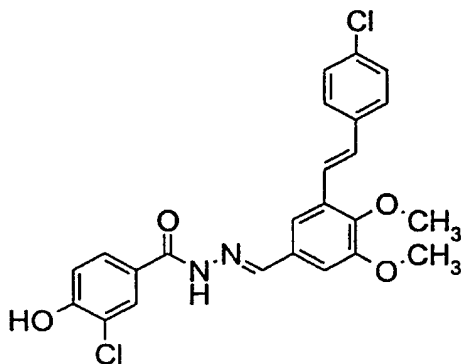
## EXAMPLE 622:

3-Chloro-4-hydroxybenzoic acid {3,4-dimethoxy-5-[2-(toluene-4-sulfonyl)vinyl]-benzylidene}hydrazide



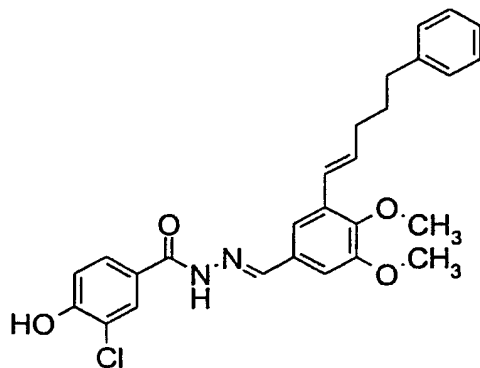
## EXAMPLE 623:

3-Chloro-4-hydroxybenzoic acid {3-[2-(4-chlorophenyl)vinyl]-4,5-dimethoxybenzylidene}hydrazide



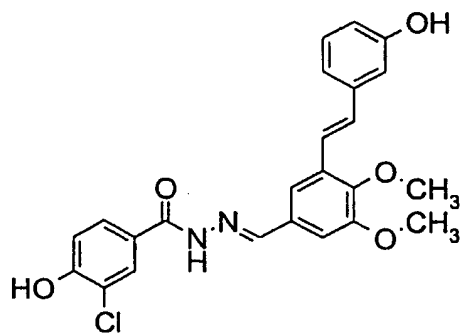
## EXAMPLE 625:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(5-phenyl-1-pentenyl)-benzylidene]hydrazide



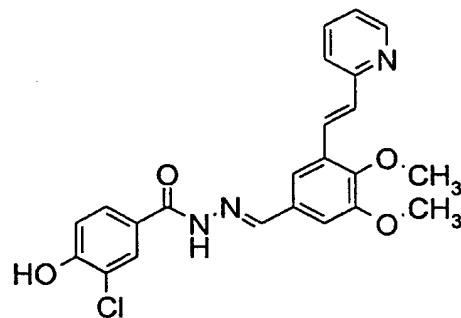
## EXAMPLE 624:

3-Chloro-4-hydroxybenzoic acid {3-[2-(3-hydroxyphenyl)vinyl]-4,5-dimethoxybenzylidene}hydrazide



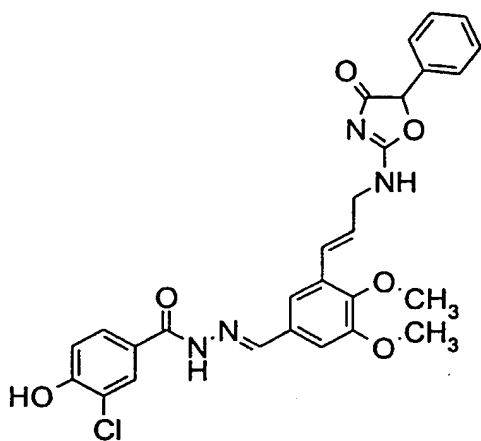
## EXAMPLE 626:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(2-(2-pyridyl)vinyl)-benzylidene]hydrazide



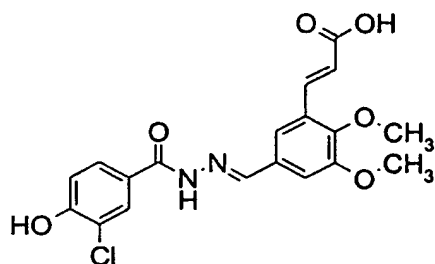
## EXAMPLE 627:

3-Chloro-4-hydroxybenzoic acid {3,4-dimethoxy-5-[3-(4-oxo-5-phenyl-4,5-dihydro-2-oxazolylamino)-1-propenyl]-benzylidene}hydrazide



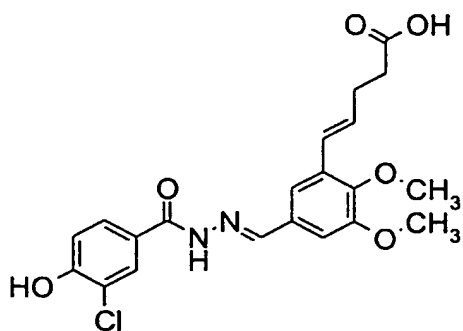
## EXAMPLE 628:

3-{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-acrylic acid



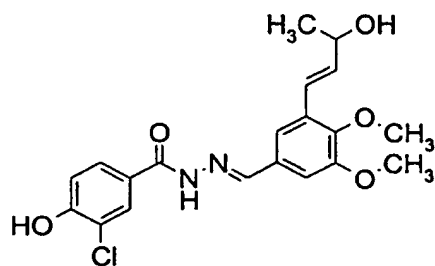
## EXAMPLE 629:

5-{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentenoic acid



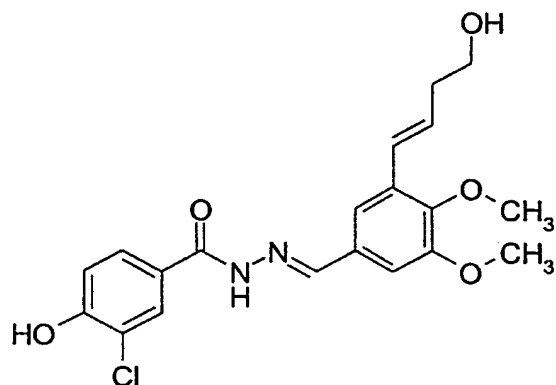
## EXAMPLE 630:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-butenyl)-4,5-dimethoxybenzylidene]hydrazide



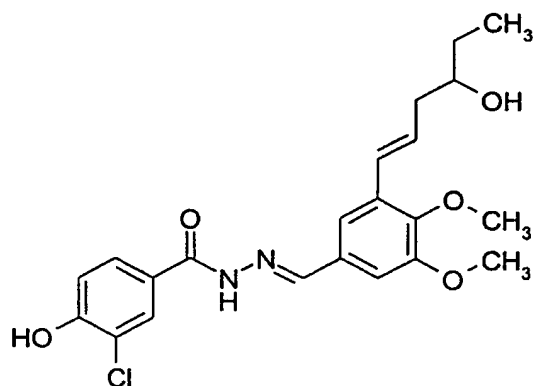
## EXAMPLE 631:

3-Chloro-4-hydroxybenzoic acid [3-(4-hydroxy-1-butenyl)-4,5-dimethoxybenzylidene]hydrazide



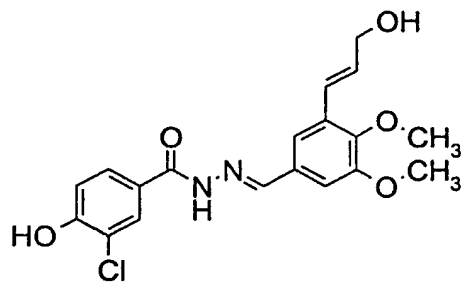
## EXAMPLE 632:

3-Chloro-4-hydroxybenzoic acid [3-(4-hydroxy-1-hexenyl)-4,5-dimethoxybenzylidene]hydrazide



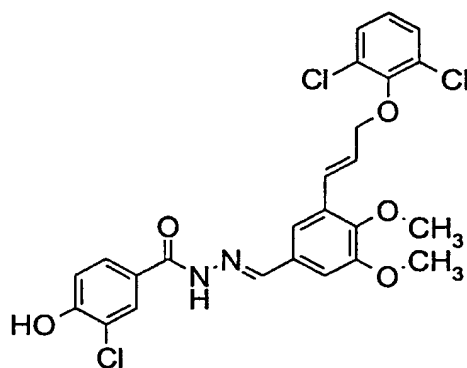
## EXAMPLE 633:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-propenyl)-4,5-dimethoxybenzylidene]hydrazide



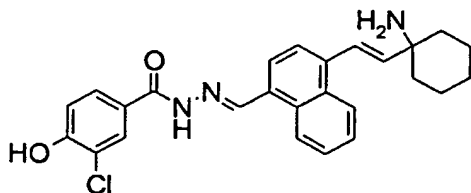
## EXAMPLE 634:

3-Chloro-4-hydroxybenzoic acid {3-[3-(2,6-dichlorophenoxy)-1-propenyl]-4,5-dimethoxybenzylidene}hydrazide



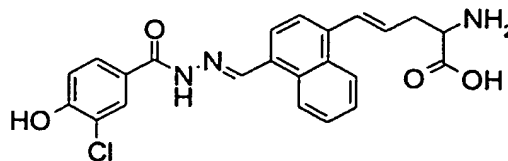
## EXAMPLE 635:

3-chloro-4-hydroxybenzoic acid {4-[2-(1-aminocyclohexyl)vinyl]-1-naphthyl-methylene}hydrazide



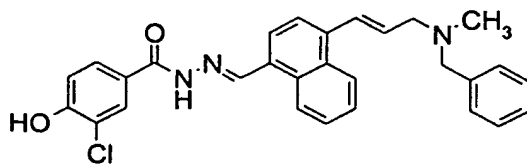
## EXAMPLE 636:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentenoic acid



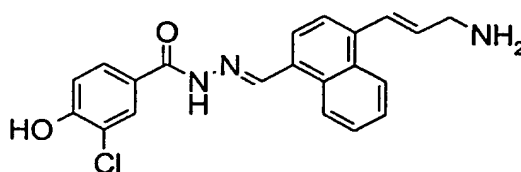
## EXAMPLE 637:

3-Chloro-4-hydroxybenzoic acid {4-[3-(benzylmethylamino)propenyl]-1-naphthylmethylene}hydrazide



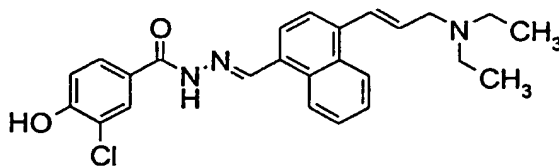
## EXAMPLE 638:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propenyl)-1-naphthylmethylene]hydrazide



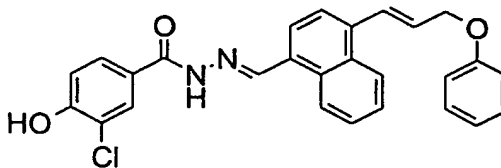
## EXAMPLE 639:

3-Chloro-4-hydroxybenzoic acid[4-(3-diethylamino-1-propenyl)-1-naphthyl-methylene]hydrazide



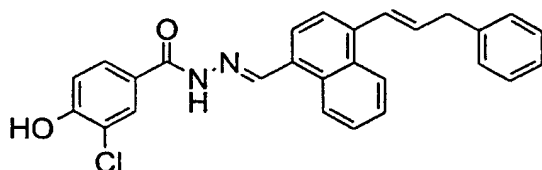
## EXAMPLE 640:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenoxy-1-propenyl)-1-naphthyl-methylene]hydrazide



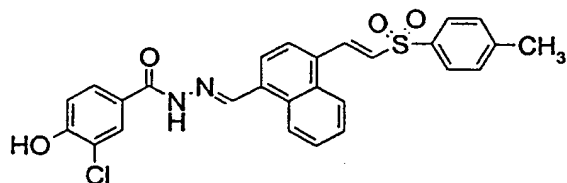
## EXAMPLE 641:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenyl-1-propenyl)-1-naphthylmethylene]hydrazide



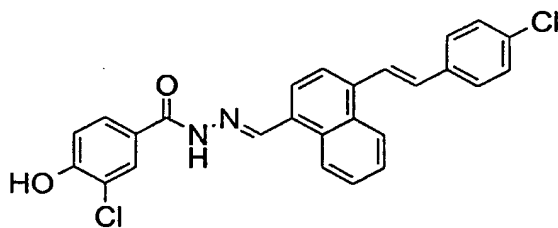
## EXAMPLE 642:

3-Chloro-4-hydroxybenzoic acid {4-[2-(toluene-4-sulfonyl)vinyl]-1-naphthylmethylene}hydrazide



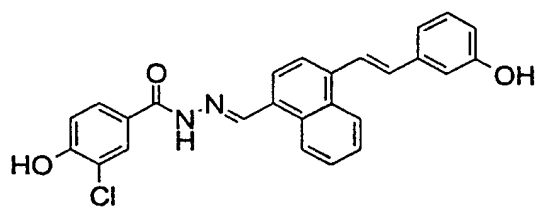
## EXAMPLE 643:

3-Chloro-4-hydroxybenzoic acid {4-[2-(4-chlorophenyl)vinyl]-1-naphthylmethylene}hydrazide



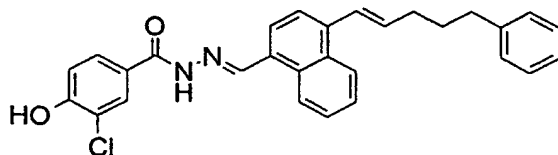
## EXAMPLE 644:

3-Chloro-4-hydroxybenzoic acid {4-[2-(3-hydroxyphenyl)vinyl]-1-naphthylmethylene}hydrazide



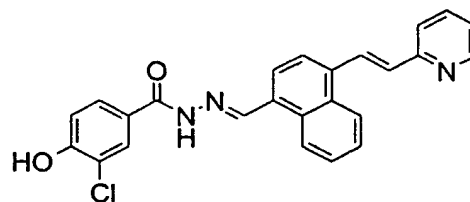
## EXAMPLE 645:

3-Chloro-4-hydroxybenzoic acid [4-(5-phenyl-1-pentenyl)-1-naphthylmethylene]hydrazide



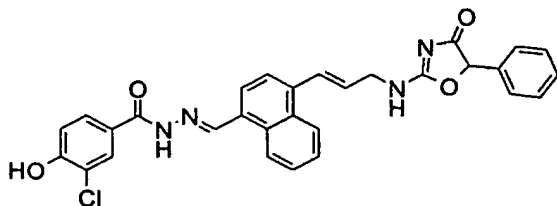
## EXAMPLE 646:

3-Chloro-4-hydroxybenzoic acid [4-(2-(2-pyridyl)vinyl)-1-naphthylmethylene]hydrazide



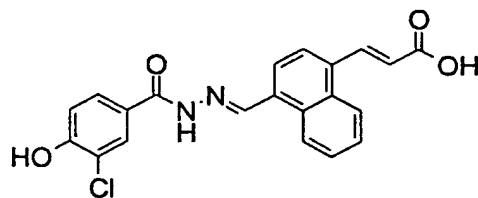
## EXAMPLE 647:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propenyl)-1-naphthylmethylene]hydrazide



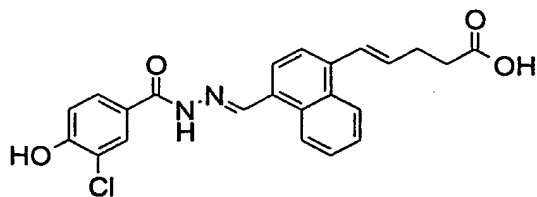
## EXAMPLE 648:

3-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}acrylic acid



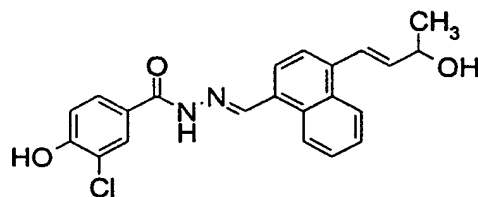
## EXAMPLE 649:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentenoic acid



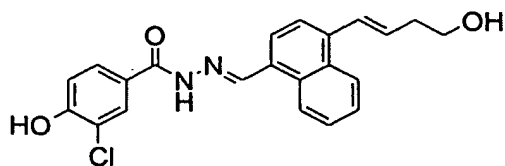
## EXAMPLE 650:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-butenyl)-1-naphthylmethylene]-hydrazide



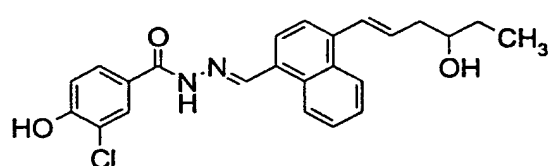
## EXAMPLE 651:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-butenyl)-1-naphthylmethylene]-hydrazide



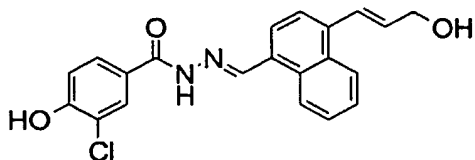
## EXAMPLE 652:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-hexenyl)-1-naphthylmethylene]hydrazide



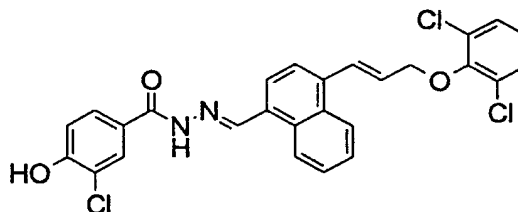
## EXAMPLE 653:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-propenyl)-1-naphthylmethylene]hydrazide



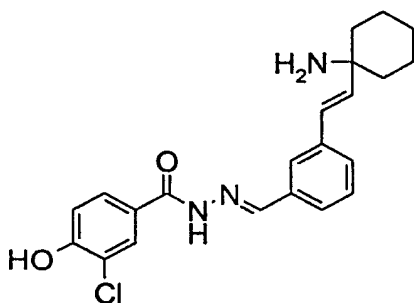
## EXAMPLE 654:

3-Chloro-4-hydroxybenzoic acid {4-[3-(2,6-dichlorophenoxy)-1-propenyl]-1-naphthylmethylene}hydrazide



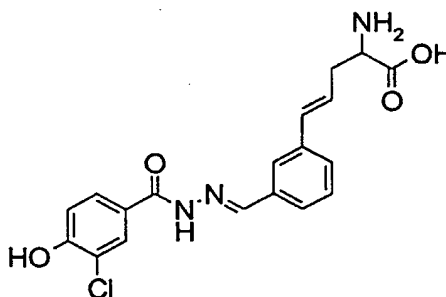
## EXAMPLE 655:

3-Chloro-4-hydroxybenzoic acid {3-[2-(1-aminocyclohexyl)vinyl]benzylidene}hydrazide



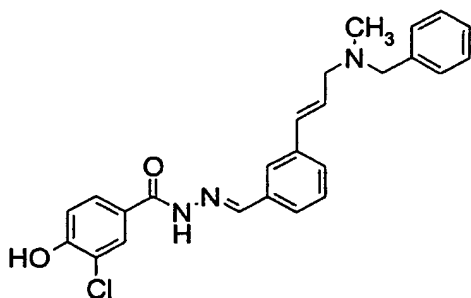
## EXAMPLE 656:

2-Amino-5-{3-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]phenyl}-4-pentenoic acid



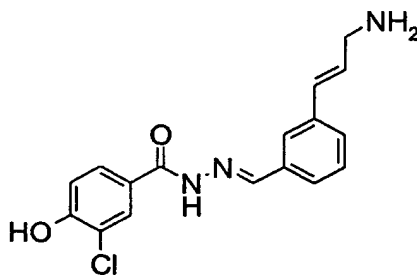
## EXAMPLE 657:

3-Chloro-4-hydroxybenzoic acid {3-[3-(benzylmethylamino)-1-propenyl]-benzylidene}hydrazide



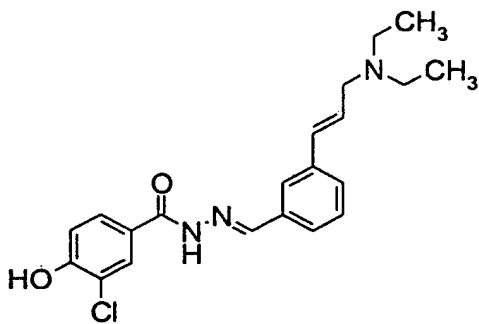
## EXAMPLE 658:

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propenyl)benzylidene]hydrazide



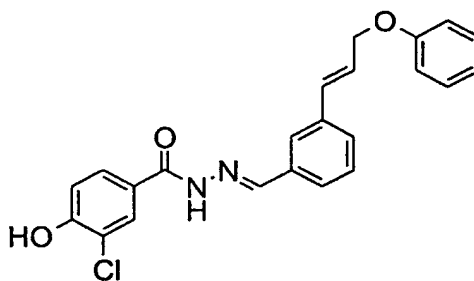
## EXAMPLE 659:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propenyl)benzylidene]-hydrazide



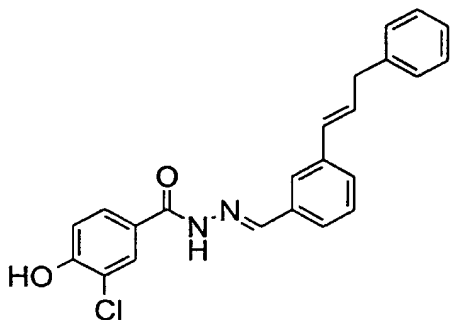
## EXAMPLE 660:

3-Chloro-4-hydroxybenzoic acid [3-(3-phenoxy-1-propenyl)benzylidene]hydrazide



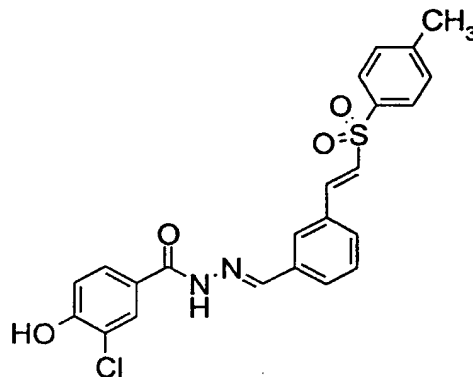
## EXAMPLE 661:

3-Chloro-4-hydroxybenzoic acid [3-(3-phenyl-1-propenyl)benzylidene]hydrazide



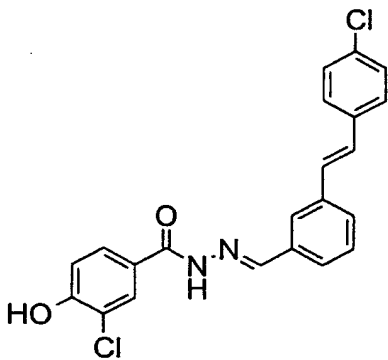
## EXAMPLE 662:

3-Chloro-4-hydroxybenzoic acid {3-[2-(toluene-4-sulfonyl)vinyl]benzylidene}hydrazide



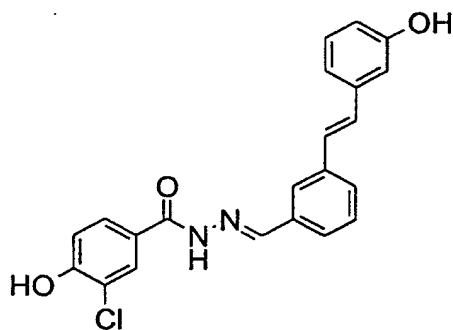
## EXAMPLE 663:

3-Chloro-4-hydroxybenzoic acid {3-[2-(4-chlorophenyl)vinyl]benzylidene}hydrazide



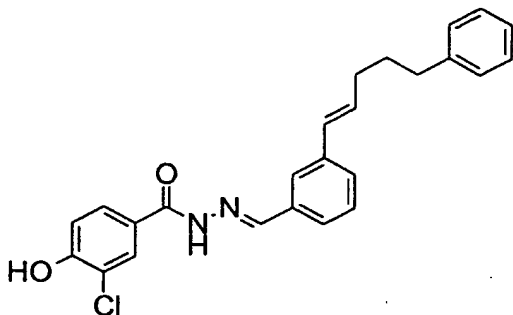
## EXAMPLE 664:

3-Chloro-4-hydroxybenzoic acid {3-[2-(3-hydroxyphenyl)vinyl]benzylidene}hydrazide



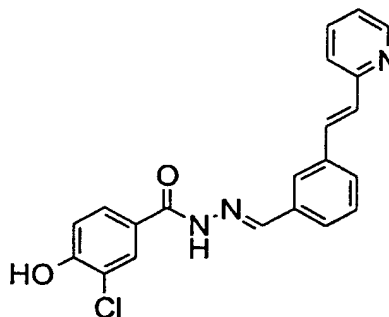
## EXAMPLE 665:

3-Chloro-4-hydroxybenzoic acid [3-(5-phenyl-1-pentenyl)benzylidene]hydrazide



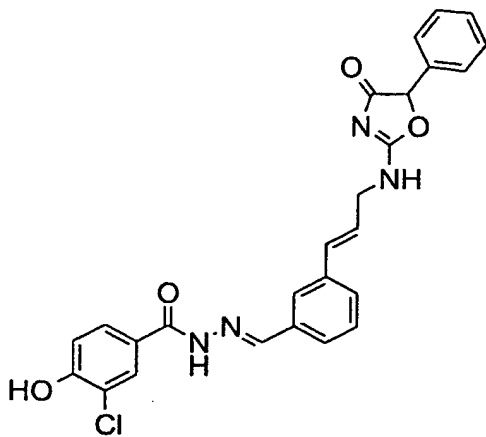
## EXAMPLE 666:

3-Chloro-4-hydroxybenzoic acid [3-(2-(2-pyridyl)vinyl)benzylidene]hydrazide



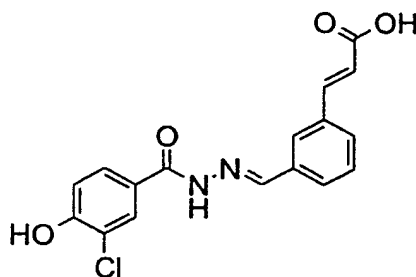
## EXAMPLE 667:

3-Chloro-4-hydroxybenzoic acid {3-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino))-1-propenyl]benzylidene}hydrazide



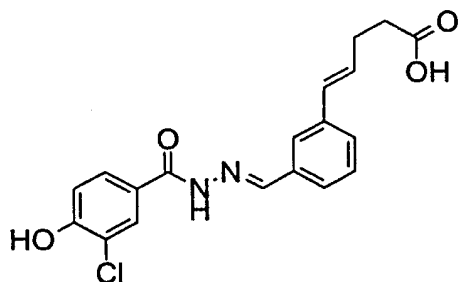
## EXAMPLE 668:

3-{3-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}acrylic acid



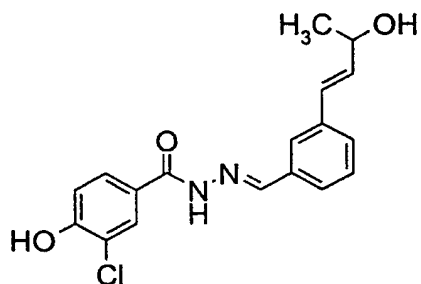
## EXAMPLE 669:

5-{3-[(3-Chloro-4-hydroxybenzoyl)-  
hydrazonomethyl]phenyl}-4-pentenoic acid



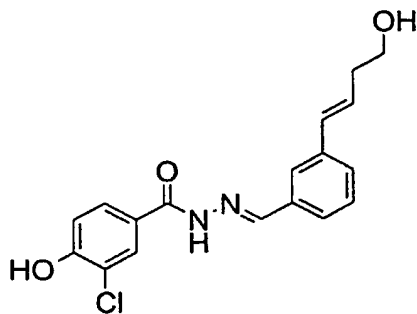
## EXAMPLE 670:

3-Chloro-4-hydroxybenzoic acid [3-(3-  
hydroxy-1-butenyl)benzylidene]hydrazide



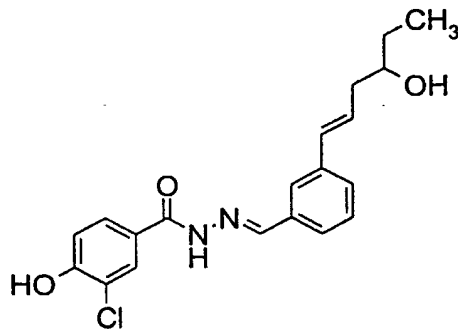
## EXAMPLE 671:

3-Chloro-4-hydroxybenzoic acid [3-(4-  
hydroxy-1-butenyl)benzylidene]hydrazide



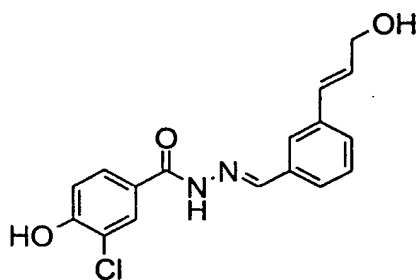
## EXAMPLE 672:

3-Chloro-4-hydroxybenzoic acid [3-(4-  
hydroxy-1-hexenyl)benzylidene]hydrazide



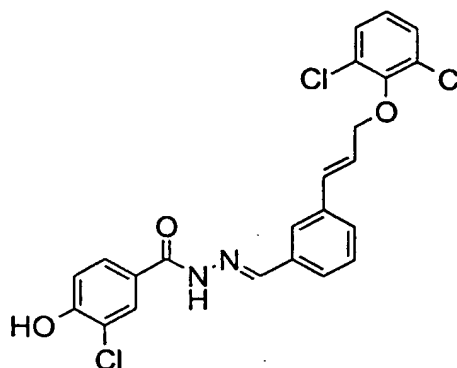
## EXAMPLE 673:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-propenyl)benzylidene]hydrazide



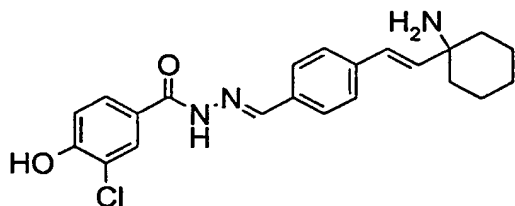
## EXAMPLE 674:

3-Chloro-4-hydroxybenzoic acid {3-[3-(2,6-dichlorophenoxy)-1-propenyl]-benzylidene}hydrazide



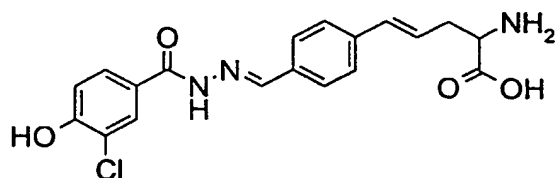
## EXAMPLE 675:

3-Chloro-4-hydroxybenzoic acid {4-[2-(1-aminocyclohexyl)vinyl]benzylidene}hydrazide



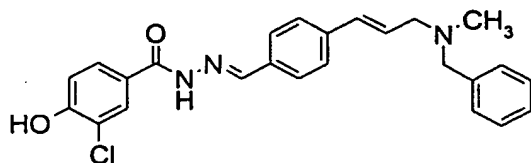
## EXAMPLE 676:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentenoic acid



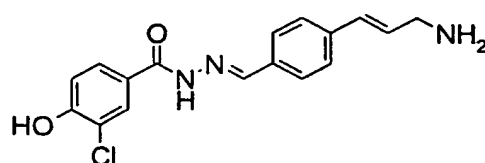
## EXAMPLE 677:

3-Chloro-4-hydroxybenzoic acid {4-[3-(benzylmethylamino)-1-propenyl]-benzylidene}hydrazide



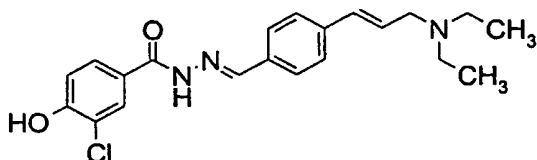
## EXAMPLE 678:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propenyl)benzylidene]hydrazide



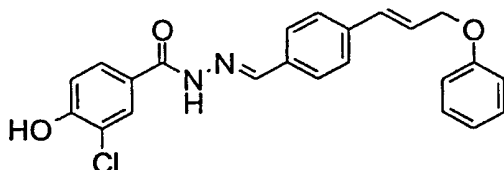
## EXAMPLE 679:

3-Chloro-4-hydroxybenzoic acid [4-(3-diethylaminopropenyl)benzylidene]hydrazide



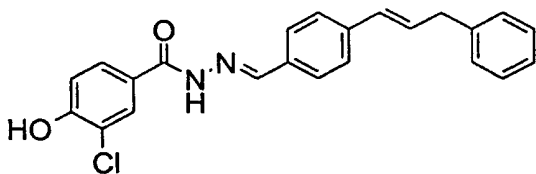
## EXAMPLE 680:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenoxy-1-propenyl)benzylidene]hydrazide



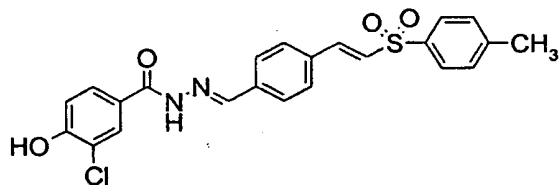
## EXAMPLE 681:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenyl-1-propenyl)benzylidene]hydrazide



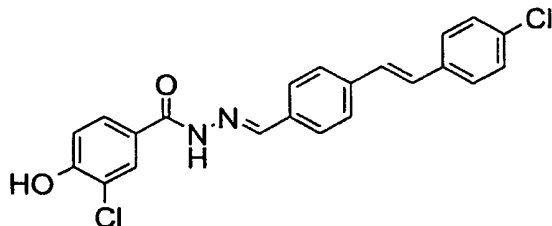
## EXAMPLE 682:

3-Chloro-4-hydroxybenzoic acid {4-[2-(toluene-4-sulfonyl)vinyl]benzylidene}hydrazide



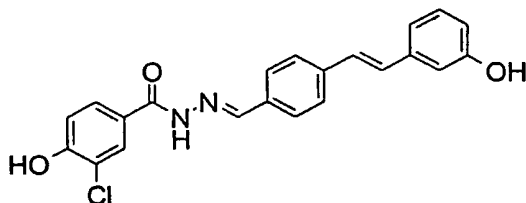
## EXAMPLE 683:

3-Chloro-4-hydroxybenzoic acid {4-[2-(4-chlorophenyl)vinyl]benzylidene}hydrazide



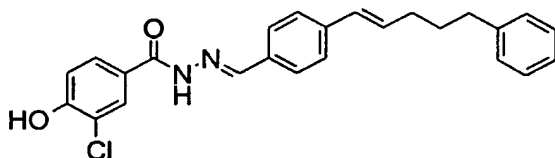
## EXAMPLE 684:

3-Chloro-4-hydroxybenzoic acid {4-[2-(3-hydroxyphenyl)vinyl]benzylidene}hydrazide



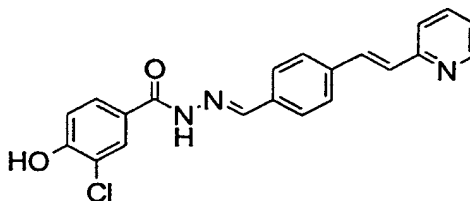
## EXAMPLE 685:

3-Chloro-4-hydroxybenzoic acid [4-(5-phenyl-1-pentenyl)benzylidene]hydrazide



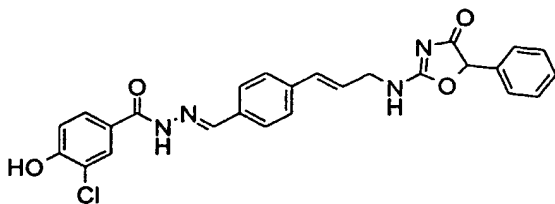
## EXAMPLE 686:

3-Chloro-4-hydroxybenzoic acid {4-[2-(2-pyridinyl)vinyl]benzylidene}hydrazide



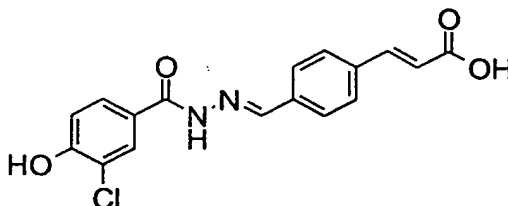
## EXAMPLE 687:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propenyl)benzylidene]hydrazide



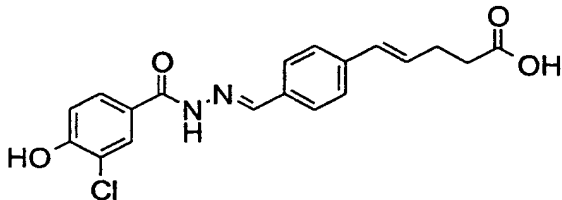
## EXAMPLE 688:

{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}acrylic acid



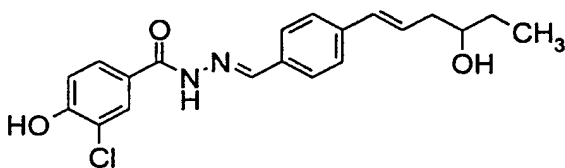
## EXAMPLE 689:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentenoic acid



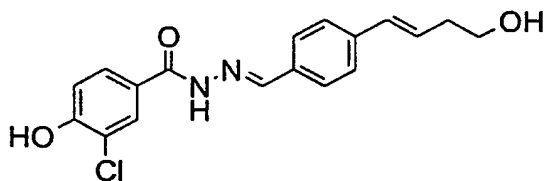
## EXAMPLE 690:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-hexenyl)benzylidene]hydrazide



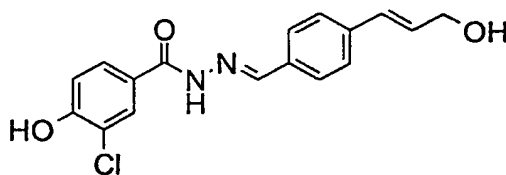
## EXAMPLE 691:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-butenyl)benzylidene]hydrazide



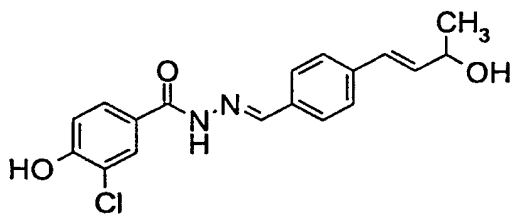
## EXAMPLE 692:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-propenyl)benzylidene]hydrazide



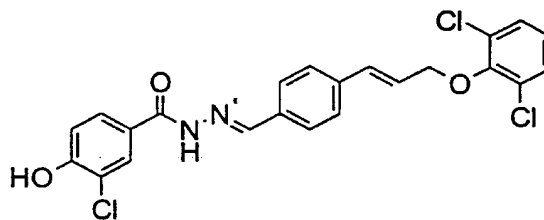
## EXAMPLE 693:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-butenyl)benzylidene]hydrazide



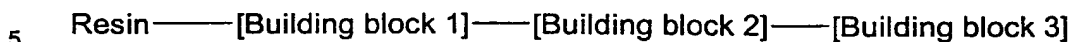
## EXAMPLE 694:

3-Chloro-4-hydroxybenzoic acid {4-[3-(2,6-dichlorophenoxy)-1-propenyl]benzylidene}hydrazide



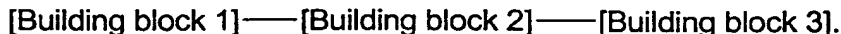
General Procedure for Examples 695 to 701:

The compounds were prepared as single entities according to the following equation



and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

10

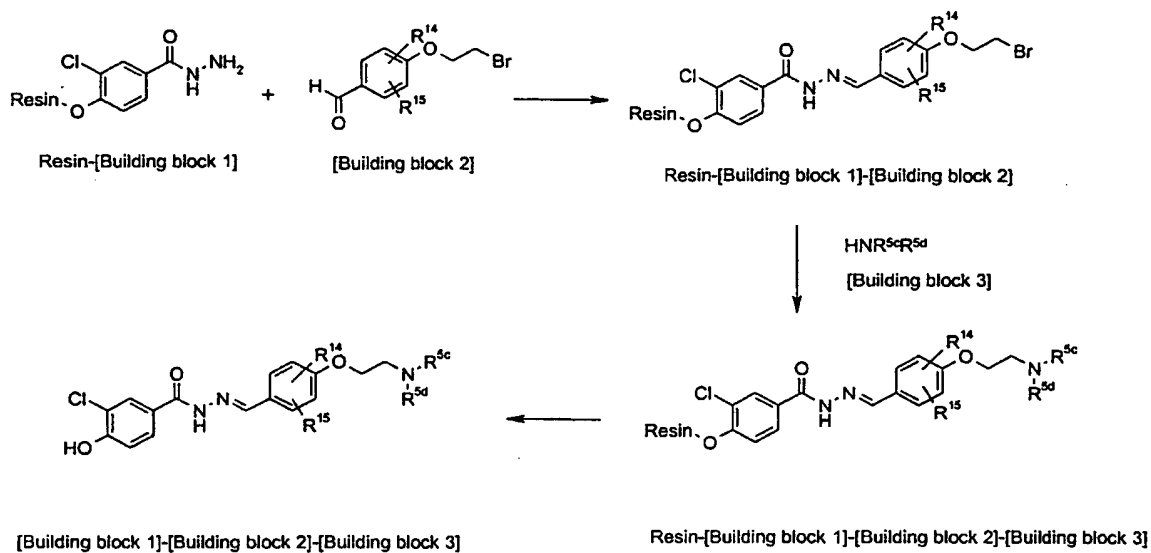


The following compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1] was done manually, whereas the attachment  
15 of [Building block 2] and [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

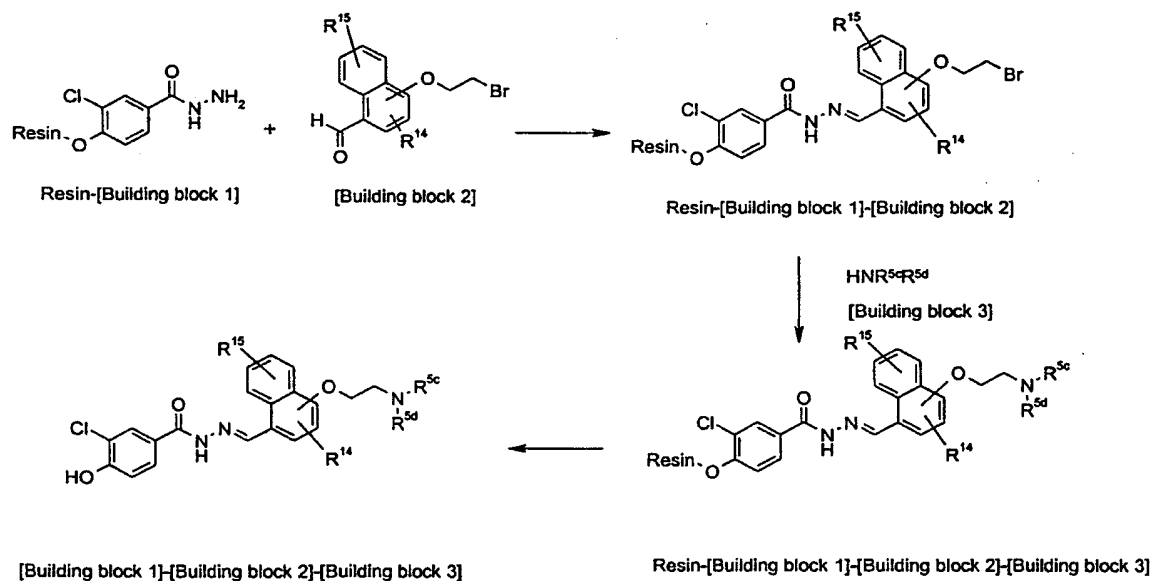
The starting resin, Resin-[Building block 1], was prepared as described above.

20 The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

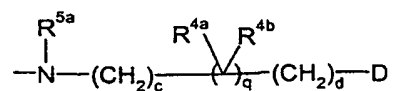
All compounds are based on successive attachment of [Building block 2] and [Building block 3] to Resin-[Building block 1] in a combinatorial way using a nucleophilic substitution reaction  
25 according to the following formulae, which are included in the general formula II:



and



- 5 wherein  $R^{14}$ ,  $R^{15}$  are as defined for formula I and  $-\text{NR}^{5c}\text{R}^{5d}$  is

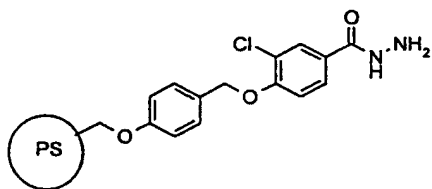


where  $R^{5a}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $c$ ,  $q$ ,  $d$ , and  $D$  are as defined for formula I or

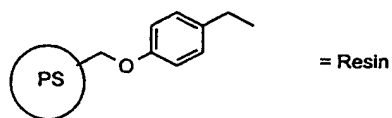
-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

The following resin, here depicted as Resin-[Building block 1] was used:

5

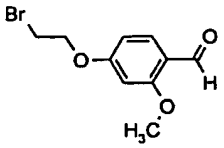
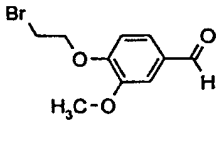
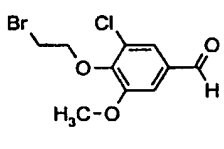
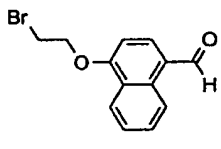
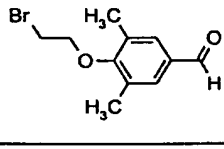
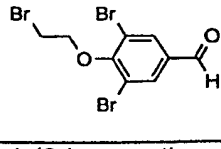
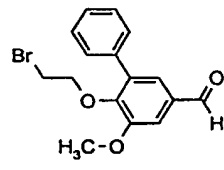
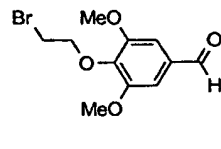


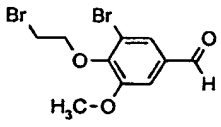
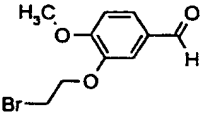
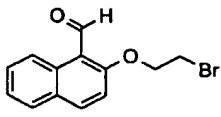
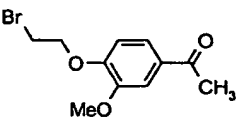
where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:



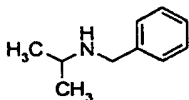
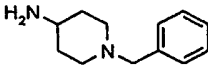
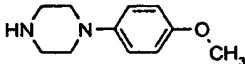
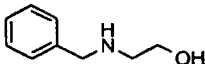
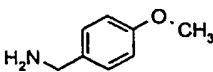
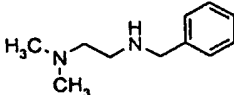
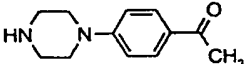
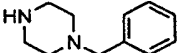
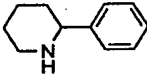
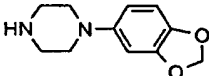
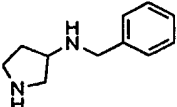
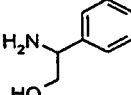
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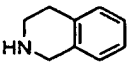
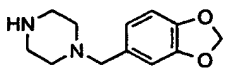
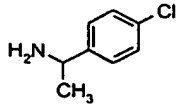
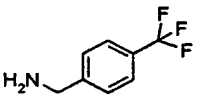
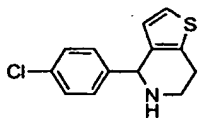
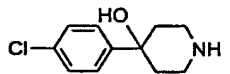
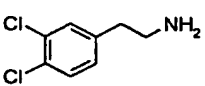
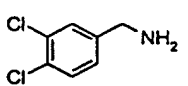
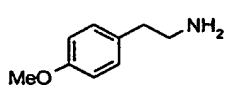
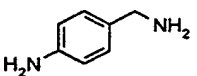
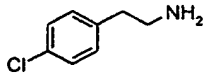
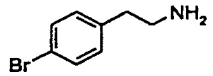
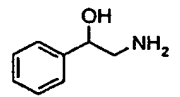
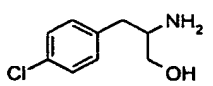
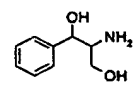
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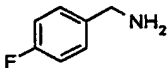
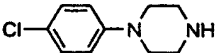
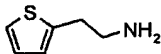
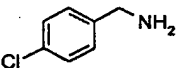
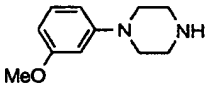
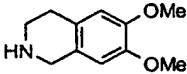
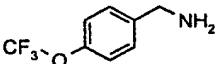
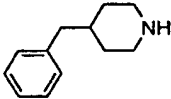
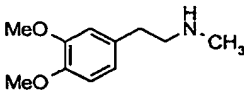
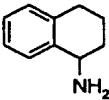
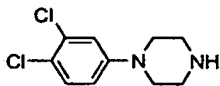
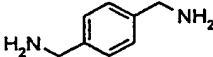
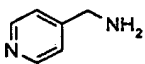
<p>4-(2-bromoethoxy)-2-methoxybenzaldehyde</p> 	<p>4-(2-bromoethoxy)-3-methoxybenzaldehyde</p> 
<p>4-(2-bromoethoxy)-3-chloro-5-methoxybenzaldehyde</p> 	<p>4-(2-bromoethoxy)-1-naphthaldehyde</p> 
<p>4-(2-bromoethoxy)-3,5-dimethylbenzaldehyde</p> 	<p>4-(2-bromoethoxy)-3,5-dibromobenzaldehyde</p> 
<p>4-(2-bromoethoxy)-3-methoxy-5-phenylbenzaldehyde</p> 	<p>4-(2-bromoethoxy)-3,5-dimethoxybenzaldehyde</p> 

<p>4-(2-bromoethoxy)-3-bromo-5-methoxybenzaldehyde</p> 	<p>3-(2-bromoethoxy)-4-methoxybenzaldehyde</p> 
<p>2-(2-bromoethoxy)-1-naphthaldehyde</p> 	<p>4-(2-bromoethoxy)-3-methoxyacetophenone</p> 

[Building block 3]:

<p>N-isopropylbenzylamine</p> 	<p>4-amino-1-benzylpiperidine</p> 	<p>1-(4-methoxyphenyl)-piperazine</p> 
<p>N-benzyl-ethanolamine</p> 	<p>4-methoxybenzylamine</p> 	<p>N'-benzyl-N,N-dimethylethylenediamine</p> 
<p>1-(4-acetylphenyl)-piperazine</p> 	<p>1-benzylpiperazine</p> 	<p>2-phenylpiperidine</p> 
<p>1-(3,4-methylenedioxyphenyl)-piperazine</p> 	<p>3-benzylaminopyrrolidine</p> 	<p>2-amino-2-phenylethanol</p> 

1,2,3,4-tetrahydroisoquinoline 	1-(3,4-methylenedioxybenzyl)-piperazine 	4-chloro-α-methylbenzylamine 
4-(trifluoromethyl)-benzylamine 	4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine 	4-(4-chlorophenyl)-4-hydroxypiperidine 
3,4-dichlorophenethylamine 	3,4-dichlorobenzylamine 	4-methoxyphenethylamine 
4-aminobenzylamine 	4-chlorophenethylamine 	4-bromophenethylamine 
2-amino-1-phenylethanol 	2-amino-3-(4-chlorophenyl)-1-propanol 	2-amino-1-phenyl-1,3-propanediol 

4-fluorobenzylamine 	1-(4-chlorophenyl)-piperazine 	2-(2-thienyl)ethylamine 
4-chlorobenzylamine 	1-(3-methoxyphenyl)-piperazine 	6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 
4-trifluoromethoxybenzylamine 	4-benzylpiperidine 	2-(3,4-dimethoxyphenyl)-N-methylethylamine 
1,2,3,4-tetrahydro-1-naphthylamine 	1-(3,4-dichlorophenyl)-piperazine 	1,4-bis(aminomethyl)-benzene 
4-(aminomethyl)pyridine 		

Preparation of resin-[Building block 1]:

5

This resin was prepared as described above.

Preparation of [Building block 2]:

10

Preparation of 4-(2-bromoethoxy)-2-methoxybenzaldehyde:

1,2-Dibromoethane (57 mL, 0.66 moles) was added to a mixture of 4-hydroxy-2-methoxybenzaldehyde (10 g, 66 mmoles) and potassium carbonate (45 g, 0.33 moles) in

DMF (130 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.8 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (400 mL), dried over  $\text{MgSO}_4$  and evaporated in vacuo to afford 17.4 g (99%) of 4-(2-bromoethoxy)-2-methoxybenzaldehyde, M.p. 78 - 79 °C.

Preparation of 4-(2-bromoethoxy)-3-methoxybenzaldehyde:

1,2-Dibromoethane (57 mL, 0.66 moles) was added to a mixture of 4-hydroxy-3-methoxybenzaldehyde (10 g, 66 mmoles) and potassium carbonate (45 g, 0.33 moles) in DMF (130 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (1.2 L) and extracted with ethyl acetate (500 + 4 x 300 mL). The combined organic phases were washed with saturated sodium chloride (500 mL), dried over  $\text{MgSO}_4$  and evaporated in vacuo to afford 16.3 g (95%) of 4-(2-bromoethoxy)-3-methoxybenzaldehyde. M.p. 61 - 64 °C.

Preparation of 4-(2-bromoethoxy)-3-chloro-5-methoxybenzaldehyde:

1,2-Dibromoethane (46 mL, 0.54 moles) was added to a mixture of 3-chloro-4-hydroxy-5-methoxybenzaldehyde (10 g, 54 mmoles) and potassium carbonate (37 g, 0.27 moles) in DMF (180 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with saturated sodium chloride (150 mL), dried over  $\text{MgSO}_4$  and evaporated in vacuo to afford 9.33 g (59%) of 4-(2-bromoethoxy)-3-chloro-5-methoxybenzaldehyde. M.p. 52 - 54 °C.

Preparation of 4-(2-bromoethoxy)-3,5-dimethylbenzaldehyde:

1,2-Dibromoethane (26 mL, 0.3 moles) was added to a mixture of 3,5-dimethyl-4-hydroxybenzaldehyde (4.57 g, 30 mmoles) and potassium carbonate (21 g, 150 mmoles) in DMF (90 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.3 L), added saturated sodium chloride (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed

with saturated sodium chloride (300 mL), dried over  $\text{MgSO}_4$  and evaporated in vacuo to afford 8.2 g (95%) of 4-(2-bromoethoxy)-3,5-dimethylbenzaldehyde as an oil.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.33 (6H, s), 3.83 (2H, t), 4.18 (2H, t), 7.60 (2H, s), 9.88 (1H, s).

Preparation of 4-(2-bromoethoxy)-3,5-dibromobenzaldehyde:

1,2-Dibromoethane (62 mL, 0.72 moles) was added to a mixture of 3,5-dibromo-4-hydroxybenzaldehyde (10 g, 36 mmol) and potassium carbonate (25 g, 180 mmol) in DMF (100 mL) and the resulting mixture was stirred vigorously at 70 °C for 16 hours. After cooling, the mixture was poured into water (300 mL) and extracted with ethyl acetate (400 mL). Water (200 mL) was added to the aqueous phase and this was extracted with ethyl acetate (150 mL). The combined organic phases were washed with saturated sodium chloride (3 x 150 mL), dried over  $\text{MgSO}_4$  and evaporated in vacuo. The residue was dissolved in refluxing 96% ethanol (60 mL). Water (15 mL) was added and after cooling, filtration, washing with 60% ethanol and drying 10.7 g (77%) of 4-(2-bromoethoxy)-3,5-dibromobenzaldehyde was isolated in two crops. M.p. 84 - 85 °C.

Preparation of 4-(2-bromoethoxy)-3-methoxy-5-phenylbenzaldehyde:

A mixture of 4-hydroxy-3-iodo-5-methoxybenzaldehyde (20 g, 72 mmol), ethylene glycol (8.0 mL, 144 mmol), and chlorotrimethylsilane 36.5 mL, 0.29 moles) in dichloromethane (300 mL) was heated at reflux for 16 hours. The mixture was cooled to room temperature and washed with saturated sodium hydrogencarbonate (3 x 200 mL). The combined aqueous phases were extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with saturated sodium chloride (200 mL), dried over  $\text{MgSO}_4$  and evaporated in vacuo to afford 22.1 g (95%) of 4-[1,3]dioxolan-2-yl-2-iodo-6-methoxy-phenol. M.p. 120 - 121 °C.

Under  $\text{N}_2$ , tetrakis-triphenylphosphinepalladium(0) was added to a mixture of the above dioxolane (10 g, 31 mmol), benzenboronic acid (4.5 g, 37 mmol), toluene (67 mL), 2 M aqueous sodium carbonate (33 mL) and methanol (20 mL). The resulting mixture was

heated at reflux under N<sub>2</sub> for 16 hours. After cooling the mixture was diluted with water (150 mL) and washed with heptane (400 mL). The aqueous phase was made acidic with 3N hydrochloric acid and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel (800 mL) eluting with a mixture of ethyl acetate and heptane (1:2) to afford 5.49 g (77%) of 4-hydroxy-3-methoxy-5-phenylbenzaldehyde. M.p. 107 - 108 °C.

1,2-Dibromoethane (41 mL, 0.48 moles) was added to a mixture of the above 4-hydroxy-3-methoxy-5-phenylbenzaldehyde (5.49 g, 24 mmoles) and potassium carbonate (17 g, 123 mmoles) in DMF (80 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (200 mL), dried over MgSO<sub>4</sub> and evaporated *in vacuo* to afford 8.1 g (100%) of 4-(2-bromoethoxy)-3-methoxy-5-phenylbenzaldehyde as an oil.

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): δ = 3.50 (2H, t), 3.96 (3H, s), 4.19 (2H, t), 7.4-7.6 (11H, m).

Preparation of 4-(2-bromoethoxy)-1-naphthaldehyde:

1,2-Dibromoethane (30 mL, 0.35 moles) was added to a mixture of 4-hydroxy-1-naphthaldehyde (6 g, 35 mmoles) and potassium carbonate (24 g, 175 mmoles) in DMF (110 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.5 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (300 mL), dried over MgSO<sub>4</sub> and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (800 mL) eluting with a mixture of ethyl acetate and heptane (1:1) to afford 8.5 g (88%) of 4-(2-bromoethoxy)-1-naphthaldehyde as a solid. M.p.: 83 - 84 °C.

Calculated for C<sub>13</sub>H<sub>11</sub>BrO<sub>2</sub>: C, 55.94%; H, 3.97%.

Found: C, 56.10%; H, 3.98%; C, 56.30%; H, 3.97%.

Preparation of 4-(2-bromoethoxy)-3,5-dimethoxybenzaldehyde:

1,2-Dibromoethane (47 mL, 0.55 moles) was added to a mixture of syringaldehyde (10 g, 55 mmol) and potassium carbonate (38 g, 275 mmol) in DMF (150 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.5 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (500 mL), dried over MgSO<sub>4</sub> and evaporated in vacuo to afford 3.44 g (22%) of 4-(2-bromoethoxy)-3,5-dimethoxybenzaldehyde.

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): δ = 3.70 (2H, t), 3.88 (3H, s), 4.27 (2H, t), 7.27 (2H, s).

Preparation of 3-(2-bromoethoxy)-4-methoxybenzaldehyde:

1,2-Dibromoethane (56 mL, 0.66 moles) was added to a mixture of 3-hydroxy-4-methoxybenzaldehyde (10 g, 66 mmol) and potassium carbonate (45 g, 328 mmol) in DMF (170 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.5 L) and extracted with ethyl acetate (3 x 200 mL). The combined organic phases were washed with saturated sodium chloride (500 mL), dried over MgSO<sub>4</sub> and evaporated in vacuo. The residue was purified by column chromatography on silica gel (800 mL) eluting with a mixture of ethyl acetate and heptane (1:1) to afford 9.8 g (58%) of 3-(2-bromoethoxy)-4-methoxybenzaldehyde.

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): δ = 3.82 (2H, t), 3.90 (3H, s), 4.40 (2H, t), 7.22 (1H, d), 7.44 (1H, d), 7.59 (1H, dd).

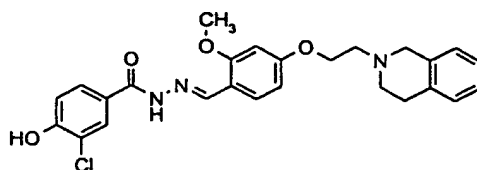
Preparation of 4-(2-bromoethoxy)-3-bromo-5-methoxybenzaldehyde:

1,2-Dibromoethane (37 mL, 0.43 moles) was added to a mixture of 5-bromovanillin (10 g, 43 mmol) and potassium carbonate (30 g, 216 mmol) in DMF (150 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours followed by vigorously stirring at 60 °C for 16 hours. The cooled mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 250 mL). The combined organic phases were washed with saturated sodium chloride (300 mL), dried over MgSO<sub>4</sub> and evaporated in vacuo to afford 13.7 g (94%) of 4-(2-bromoethoxy)-3-bromo-5-methoxybenzaldehyde.

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): δ = 3.79 (2H, t), 3.93 (3H, s), 4.40 (2H, t), 7.55 (1H, d), 7.79 (1H, d).

5 EXAMPLE 695:

Preparation of 3-Chloro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]-2-methoxybenzylidene}hydrazide



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The resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block1]) (3 g, ~3 mmoles) was swelled in DMF (35 mL) for 30 minutes. Then 4-(2-bromoethoxy)-2-methoxybenzaldehyde (2.33 g, 9 mmoles) and triethyl orthoformate (18 mL) were added and the mixture was shaken at room temperature for 16 hours. The resin was repeatedly swelled  
15 in DMF (35 ml, 4 times), CH<sub>2</sub>Cl<sub>2</sub> (35 mL, 6 times) and N-methyl-2-pyrrolidinone (NMP) (35 mL, 2 times) and filtered. The resin was swelled in NMP (40 mL) and 1,2,3,4-tetrahydroisoquinoline (3.75 mL, 30 mmoles) and potassium iodide (1.0 g, 6 mmoles) were added. The resin was shaken at room temperature for 16 hours and filtered. The resin was repeatedly swelled in DMF (40 ml, 5 times), CH<sub>2</sub>Cl<sub>2</sub> (40 mL, 10 times) and filtered. The compound was cleaved off the resin by shaking for 1 hour at room temperature with a 50% solution of trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (40 mL). The mixture was filtered and the resin was extracted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL, 2 times). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were concentrated in vacuo. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and concentrated in vacuo. The residue was dissolved in methanol (40 mL) and concentrated in vacuo. The residue was partitioned  
25 between ethyl acetate (50 mL) and saturated sodium hydrogencarbonate (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organic extracts were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by column chromatography over silica gel (200 mL) eluting with a mixture of CH<sub>2</sub>Cl<sub>2</sub> and methanol (9:1). This afforded 280 mg of the title compound.

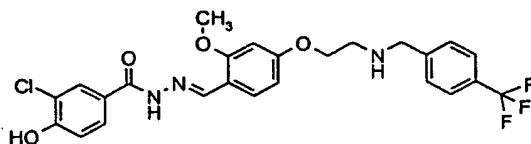
HPLC-MS (METHOD A):  $R_t$  = 8.44 min;  $m/z$  = 480 (M+1).

$^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 2.80 (4H, m), 2.90 (2H, t), 3.69 (2H, s), 3.86 (3H, s), 4.25 (2H, t), 6.68 (2H, m), 7.04 (1H, d), 7.07-7.14 (5H, m), 7.75 (1H, dd), 7.80 (1H, bs), 7.96 (1H, d), 8.58 (1H, s), 11.6 (1H, s).

HR-MS: Calcd. for  $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_4$ : 479.1611; Found: 479.1604.

10 EXAMPLE 696:

3-Chloro-4-hydroxybenzoic acid {2-methoxy-4-[2-(4-trifluoromethylbenzylamino)ethoxy]-benzylidene}hydrazide



15

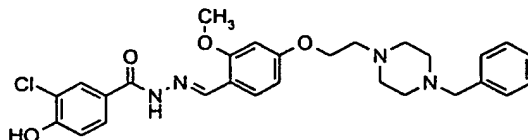
This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-2-methoxybenzaldehyde ([building block 2]) (0.73 g, 1.5 equivs.), and 4-trifluoromethylbenzylamine ([building block 3]) (3.3 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue (1 g) was purified by column chromatography on silica gel (20 g) eluting with a mixture of 25% aq. ammonia, ethanol and dichloromethane (1:9:115). This afforded 130 mg of the title compound.

25

HPLC-MS (METHOD A):  $R_t$  = 9.4 min;  $m/z$  = 522 (M+1).

EXAMPLE 697:

3-Chloro-4-hydroxybenzoic acid {4-[2-(4-benzylpiperazin-1-yl)ethoxy]-2-methoxybenzylidene}hydrazide



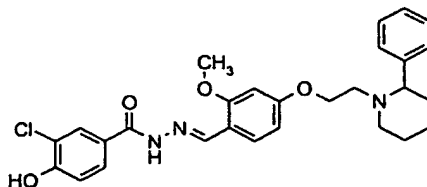
This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-2-methoxybenzaldehyde ([building block 2]) (0.73 g, 1.5 equivs.), and 1-benzylpiperazine ([building block 3]) (3.3 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue (1.4 g) was dissolved in 2-propanol (50 ml) and concentrated to 20 ml. The mixture was allowed to stand at 5 °C for 1 h and filtered. The mother liquor was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (20 g) eluting with a mixture of methanol and dichloromethane (1:9). This afforded 0.98 g of the title compound.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> = 2.4 (2H, bs), 2.55 (2H, bs), 2.62 (2H, bs), 3.50 (2H, bs), 3.85 (3H, s), 4.15 (2H, t), 6.62 (2H, m), 7.05 (1H, d), 7.30 (5H, m), 7.75 (2H, t), 7.97 (1H, s), 8.67 (1H, s), 11 (1H, bs), 11.5 (1H, s).

HPLC-MS (METHOD A): R<sub>t</sub> = 7.7 min; m/z = 523 (M+1).

#### EXAMPLE 698:

3-Chloro-4-hydroxybenzoic acid {2-methoxy-4-[2-(2-phenylpiperidin-1-yl)ethoxy]benzylidene}hydrazide



This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-2-methoxybenzaldehyde ([building block 2])

(0.73 g, 1.5 equivs.), and 2-phenylpiperidine ([building block 3]) (3.0 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue (1.0 g) was purified by column chromatography on silica gel (28 g) eluting with a mixture of methanol and dichloromethane (1:13). This afforded 0.24 g of the title compound.

5

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> = 1.4 (2H, m), 1.65 (4H, m), 2.25 (2H, m), 2.75 (1H, m), 3.16 (1H, d), 3.25 (2H, d), 3.83 (3H, s), 4.0 (2H, m), 6.50 (1H, d), 6.54 (1H, s), 7.07 (1H, d), 7.23 (1H, t), 7.35 (4H, m), 7.73 (1H, d), 7.77 (1H, dd), 7.96 (1H, d), 8.65 (1H, s), 10.9 (1H, s), 11.6 (1H, s).

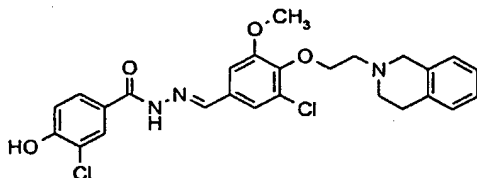
10

HPLC-MS (METHOD A): R<sub>t</sub> = 9.1 min; m/z = 508 (M+1).

#### EXAMPLE 699:

3-Chloro-4-hydroxybenzoic acid {3-chloro-4-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)ethoxy]-5-methoxybenzylidene}hydrazide

15



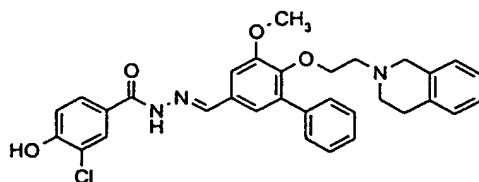
20 This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-3-chloro-5-methoxybenzaldehyde ([building block 2]) (0.81 g, 1.5 equivs.), and 1,2,3,4-tetrahydroisoquinoline ([building block 3]) (2.5 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue (1.0 g) was dissolved in  
25 15 ml of a mixture of 25% aq. ammonia, methanol and dichloromethane (1:9:90) and purified by column chromatography on silica gel (25 g) eluting with a mixture of methanol and dichloromethane (1:12). This afforded 0.11 g of the title compound.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> = 1.9 (1H, p), 2.18 (1H, t), 2.90 (2H, t), 3.70 (2H, s), 3.90 (3H, s), 4.19 (2H, t), 7.05 (5H, m), 7.37 (2H, s), 7.78 (1H, d), 7.95 (1H, s), 8.33 (1H, s), 11 (1H, bs), 11.8 (1H, s).

5 HPLC-MS (METHOD A): R<sub>t</sub> = 9.0 min; m/z = 514 (M+1).

EXAMPLE 700:

10 3-Chloro-4-hydroxybenzoic acid {6-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)ethoxy]-5-methoxybiphenyl-3-ylmethylene}hydrazide



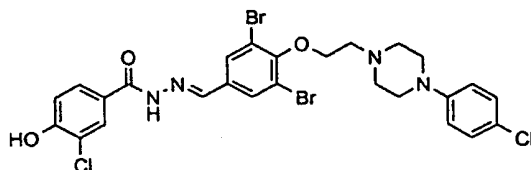
15 This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-3-methoxy-5-phenylbenzaldehyde ([building block 2]) (0.93 g, 1.5 equivs.), and 1,2,3,4-tetrahydroisoquinoline ([building block 3]) (2.5 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue was dissolved in 15 ml of a mixture of 25% aq. ammonia, methanol and dichloromethane (1:9:90) and purified by  
20 column chromatography on silica gel (25 g) eluting with a mixture of methanol and dichloromethane (1:12). This afforded 0.31 g of the title compound.

25 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> = 2.60 (4H, m), 2.70 (2H, m), 3.48 (2H, s), 3.92 (3H, s), 3.96 (2H, t), 6.98 (1H, m), 7.10 (4H, m), 7.22 (1H, s), 7.40 (4H, m), 7.55 (2H, d), 7.78 (1H, d), 8.00 (1H, s), 8.40 (1H, s), 11 (1H, bs), 11.7 (1H, s).

HPLC-MS (METHOD A): R<sub>t</sub> = 9.6 min; m/z = 557 (M+1).

EXAMPLE 701:

3-Chloro-4-hydroxybenzoic acid (3,5-dibromo-4-{2-[4-(4-chlorophenyl)piperazin-1-yl]-ethoxy}benzylidene)hydrazide



5 A solution of 4-(2-bromoethoxy)-3,5-dibromobenzaldehyde ([building block 2]) in DMF (0.6 M, 1 mL) was added to the resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (0.05 mmoles) followed by addition of triethyl orthoformate (0.5 mL) and the mixture was shaken at room temperature for 15 hours. The resin was repeatedly swelled in DMF (1.5 mL, 3 times), CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 2 times) and NMP (1.5 mL, 2 times) for 5 minutes and filtered. The resulting resin (resin-[building block 1]-[building block 2]) was added a solu-  
10 tion of 1-(4-chlorophenyl)piperazine (0.4 M, 1 mL) and a solution of potassium iodide in NMP (0.08 M, 0.5 mL) were added and the mixture was shaken at room temperature for 16 hours. The resin was repeatedly swelled in DMF (1.5 mL, 3 times) and CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 6 times) for 2 minutes and filtered.

15

The compound was cleaved off the resin by shaking for 1 hour at room temperature with a 50% solution of trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). The mixture was filtered and the resin was extracted with CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were concentrated in vacuo. The residue was dissolved in methanol (1 mL) and concentrated in vacuo. The resi-  
20 due was dissolved in a 1:1 mixture of methanol and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD B): R<sub>t</sub> = 15.02 min; m/z = 671.

25 EXAMPLES 702 TO 791 :

The following 90 compounds were prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model 384 HTS using the following ChemFile to control the operation of the synthesizer.

Further, a library of compounds of all the possible combinations of the above listed building blocks ([building block 1], [building block 2] and [building block 3]) was prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model  
5 384 HTS using the following ChemFile to control the operation of the synthesizer. The compounds are all expected to be present in the respective wells.

The resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) is equally distributed in the wells in the synthesizer prior to the initialization of the device.

10

ChemFile C:\ACT\_1328\90250012.CHM:

1 REM Filtration of resin  
2 Empty RB1\_1to96 for 5.000 minute(s)  
15 3 Empty RB2\_1to96 for 5.000 minute(s)  
4 Empty RB3\_1to96 for 5.000 minute(s)  
5 Empty RB4\_1to96 for 5.000 minute(s)  
6 Pause  
7  
20 8 REM Washing of resin  
9  
10 Dispense System Fluid Disdu1\_4\* 1500ul to RB1\_1to96[1-96]  
11 Dispense System Fluid Disdu1\_4\* 1500ul to RB2\_1to96[1-96]  
12 Dispense System Fluid Disdu1\_4\* 1500ul to RB3\_1to96[1-96]  
25 13 Dispense System Fluid Disdu1\_4\* 1500ul to RB4\_1to96[1-96]  
14 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
15 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
16 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
17 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
30 18 Wait for 25.000 minute(s)  
19 Repeat from step 14, 1000 times  
20 Empty RB1\_1to96 for 5.000 minute(s)  
21 Empty RB2\_1to96 for 5.000 minute(s)  
22 Empty RB3\_1to96 for 5.000 minute(s)  
35 23 Empty RB4\_1to96 for 5.000 minute(s)  
24 Pause  
25  
26 REM Coupling with aldehydes  
27  
40 28 Dispense System Fluid Disdu2\_3\* 1500ul to RB1\_1to96[1-96]  
29 Dispense System Fluid Disdu2\_3\* 1500ul to RB2\_1to96[1-96]  
30 Dispense System Fluid Disdu2\_3\* 1500ul to RB3\_1to96[1-96]  
31 Dispense System Fluid Disdu2\_3\* 1500ul to RB4\_1to96[1-96]

- 32 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
33 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
34 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
35 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
5 36 Empty RB1\_1to96 for 5.000 minute(s)  
37 Empty RB2\_1to96 for 5.000 minute(s)  
38 Empty RB3\_1to96 for 5.000 minute(s)  
39 Empty RB4\_1to96 for 5.000 minute(s)  
40 Pause  
10 41  
42 Dispense Sequence c:\ACT13\_28\R2-A.DSP with 1000ul to RB1\_1to96 rack using DMF  
43 Mix "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
44 Dispense Sequence c:\ACT13\_28\R2-B.DSP with 1000ul to RB2\_1to96 rack using DMF  
45 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
15 46 Mix "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
47 Dispense Sequence c:\ACT13\_28\R2-C.DSP with 1000ul to RB3\_1to96 rack using DMF  
48 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
49 Start mixing "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
50 Mix "RB3\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
20 51 Dispense Sequence c:\ACT13\_28\R2-D.DSP with 1000ul to RB4\_1to96 rack using DMF  
52 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
53 Start mixing "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
54 Start mixing "RB3\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
55 Mix "RB4\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
25 56  
57 Pause  
58 REM Manual addition of CH(OC2H5)3  
59 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
60 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
30 61 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
62 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
63 Wait for 25.000 minute(s)  
64 Repeat from step 59, 200 times  
65 Empty RB1\_1to96 for 5.000 minute(s)  
35 66 Empty RB2\_1to96 for 5.000 minute(s)  
67 Empty RB3\_1to96 for 5.000 minute(s)  
68 Empty RB4\_1to96 for 5.000 minute(s)  
69 Pause  
70  
40 71 REM Wash after coupling with aldehydes  
72  
73 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter  
74 Dispense System Fluid Disdu2\_3\* 1500ul to RB1\_1to96[1-96]  
75 Dispense System Fluid Disdu2\_3\* 1500ul to RB2\_1to96[1-96]  
45 76 Dispense System Fluid Disdu2\_3\* 1500ul to RB3\_1to96[1-96]  
77 Dispense System Fluid Disdu2\_3\* 1500ul to RB4\_1to96[1-96]  
78 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
79 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
80 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.

- 81 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
82 Empty RB1\_1to96 for 5.000 minute(s)  
83 Empty RB2\_1to96 for 5.000 minute(s)  
84 Empty RB3\_1to96 for 5.000 minute(s)  
5 85 Empty RB4\_1to96 for 5.000 minute(s)  
86 Repeat from step 74, 2 times  
87 Pause  
88 Dispense System Fluid Disdu1\_4\* 1500ul to RB1\_1to96[1-96]  
89 Dispense System Fluid Disdu1\_4\* 1500ul to RB2\_1to96[1-96]  
10 90 Dispense System Fluid Disdu1\_4\* 1500ul to RB3\_1to96[1-96]  
91 Dispense System Fluid Disdu1\_4\* 1500ul to RB4\_1to96[1-96]  
92 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
93 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
94 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
15 95 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
96 Empty RB1\_1to96 for 5.000 minute(s)  
97 Empty RB2\_1to96 for 5.000 minute(s)  
98 Empty RB3\_1to96 for 5.000 minute(s)  
99 Empty RB4\_1to96 for 5.000 minute(s)  
20 100 Repeat from step 88, 1 times  
101 Dispense System Fluid Disdu2\_3\* 1500ul to RB1\_1to96[1-96]  
102 Dispense System Fluid Disdu2\_3\* 1500ul to RB2\_1to96[1-96]  
103 Dispense System Fluid Disdu2\_3\* 1500ul to RB3\_1to96[1-96]  
104 Dispense System Fluid Disdu2\_3\* 1500ul to RB4\_1to96[1-96]  
25 105 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
106 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
107 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
108 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
109 Wait for 25.000 minute(s)  
30 110 Repeat from step 105, 1000 times  
111 Pause  
112 Empty RB1\_1to96 for 5.000 minute(s)  
113 Empty RB2\_1to96 for 5.000 minute(s)  
114 Empty RB3\_1to96 for 5.000 minute(s)  
35 115 Empty RB4\_1to96 for 5.000 minute(s)  
116 Repeat from step 101, 1 times  
117  
118 REM Coupling with amines  
119 Flush Arm1 with Disdu2\_3\*, Arm2 with Disdu2\_3\*  
40 120 Dispense Sequence c:\ACT13\_28\R3-A.DSP with 1000ul to RB1\_1to96 rack using NMP  
121 Mix "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
122 Dispense Sequence c:\ACT13\_28\R3-B.DSP with 1000ul to RB2\_1to96 rack using NMP  
123 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
124 Mix "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
45 125 Dispense Sequence c:\ACT13\_28\R3-C.DSP with 1000ul to RB3\_1to96 rack using NMP  
126 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
127 Start mixing "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
128 Mix "RB3\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
129 Dispense Sequence c:\ACT13\_28\R3-D.DSP with 1000ul to RB4\_1to96 rack using NMP

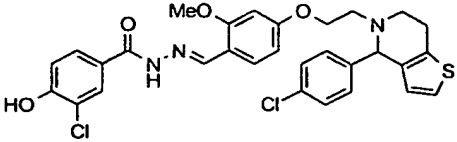
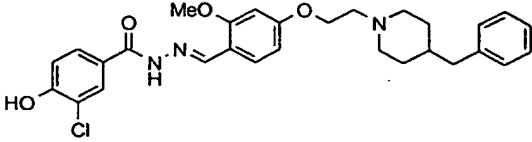
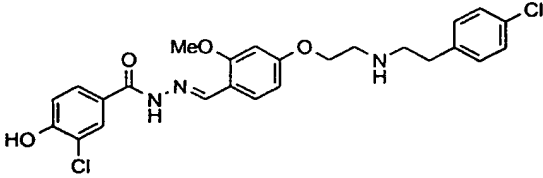
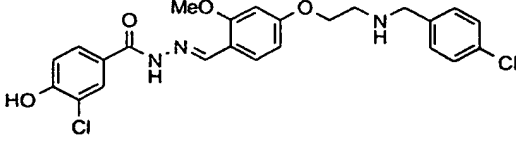
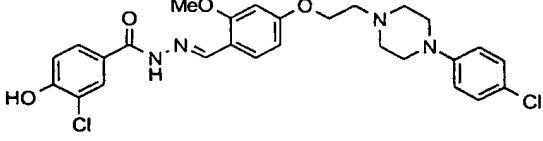
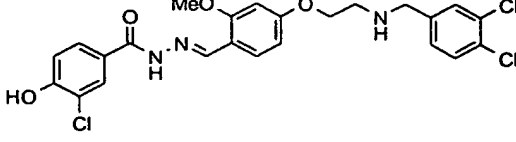
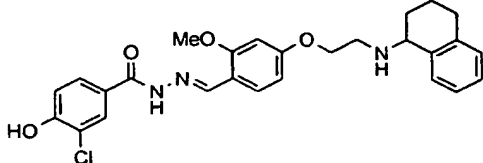
- 130 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
131 Start mixing "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
132 Start mixing "RB3\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
133 Mix "RB4\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
5 134 Pause  
135 Transfer 500ul from REAGENT\_3[1]() to RB1\_1to96[1-96] using NMP  
136 Mix "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
137 Pause  
138 Transfer 500ul from REAGENT\_3[1]() to RB2\_1to96[1-96] using NMP  
10 139 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
140 Mix "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
141 Pause  
142 Transfer 500ul from REAGENT\_3[1]() to RB3\_1to96[1-96] using NMP  
143 Start mixing "RB1\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
15 144 Start mixing "RB2\_1to96" for 2.00 minutes at 600 rpm(s) and continue.  
145 Mix "RB3\_1to96" for 2.00 minutes at 600 rpm(s) and wait.  
146 Pause  
147 Transfer 500ul from REAGENT\_3[1]() to RB4\_1to96[1-96] using NMP  
148 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
20 149 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
150 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
151 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
152 Wait for 25.000 minute(s)  
153 Repeat from step 148, 200 times  
25 154 Pause  
155  
156 Empty RB1\_1to96 for 5.000 minute(s)  
157 Empty RB2\_1to96 for 5.000 minute(s)  
158 Empty RB3\_1to96 for 5.000 minute(s)  
30 159 Empty RB4\_1to96 for 5.000 minute(s)  
160  
161  
162 REM Wash after coupling with amines  
163  
35 164 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter  
165  
166 Dispense System Fluid Disdu2\_3\* 1500ul to RB1\_1to96[1-96]  
167 Dispense System Fluid Disdu2\_3\* 1500ul to RB2\_1to96[1-96]  
168 Dispense System Fluid Disdu2\_3\* 1500ul to RB3\_1to96[1-96]  
40 169 Dispense System Fluid Disdu2\_3\* 1500ul to RB4\_1to96[1-96]  
170 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
171 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
172 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
173 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
45 174 Empty RB1\_1to96 for 5.000 minute(s)  
175 Empty RB2\_1to96 for 5.000 minute(s)  
176 Empty RB3\_1to96 for 5.000 minute(s)  
177 Empty RB4\_1to96 for 5.000 minute(s)  
178 Repeat from step 166, 2 times

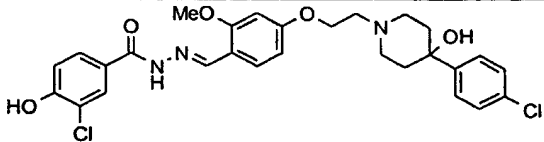
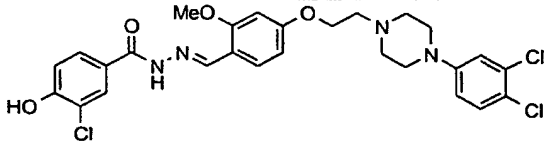
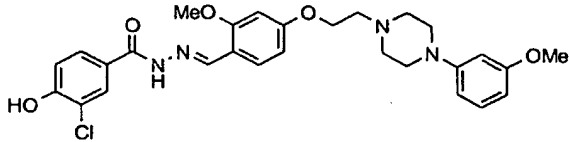
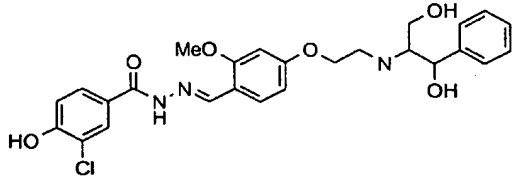
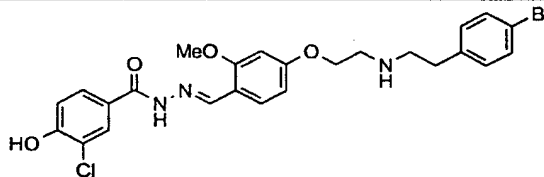
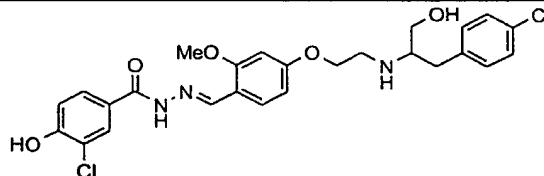
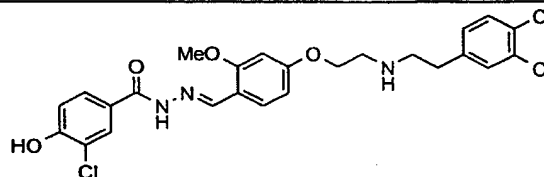
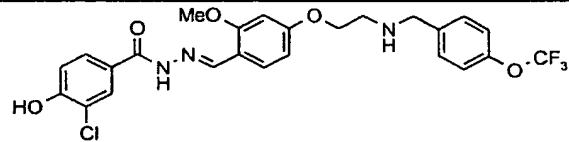
- 179 Pause  
180 Dispense System Fluid Disdu1\_4\* 1500ul to RB1\_1to96[1-96]  
181 Dispense System Fluid Disdu1\_4\* 1500ul to RB2\_1to96[1-96]  
182 Dispense System Fluid Disdu1\_4\* 1500ul to RB3\_1to96[1-96]  
5 183 Dispense System Fluid Disdu1\_4\* 1500ul to RB4\_1to96[1-96]  
184 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
185 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
186 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
187 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
10 188 Empty RB1\_1to96 for 5.000 minute(s)  
189 Empty RB2\_1to96 for 5.000 minute(s)  
190 Empty RB3\_1to96 for 5.000 minute(s)  
191 Empty RB4\_1to96 for 5.000 minute(s)  
192  
15 193 Repeat from step 180, 5 times  
194  
195 Dispense System Fluid Disdu1\_4\* 1500ul to RB1\_1to96[1-96]  
196 Dispense System Fluid Disdu1\_4\* 1500ul to RB2\_1to96[1-96]  
197 Dispense System Fluid Disdu1\_4\* 1500ul to RB3\_1to96[1-96]  
20 198 Dispense System Fluid Disdu1\_4\* 1500ul to RB4\_1to96[1-96]  
199 Start mixing "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
200 Start mixing "RB2\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
201 Start mixing "RB3\_1to96" for 5.00 minutes at 600 rpm(s) and continue.  
202 Mix "RB4\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
25 203 Wait for 25.000 minute(s)  
204 Repeat from step 199, 1000 times  
205  
206 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3  
207 Empty RB4\_1to96 for 5.000 minute(s)  
30 208 Pause  
209  
210 REM Cleavage (50%TFA/DCM manually added, one rack at a time)  
211 Flush Arm1 with Flush Diluter1, Arm2 with Flush Diluter 4  
212 Mix "RB1\_1to96" for 5.00 minutes at 600 rpm(s) and wait.  
35 213 Wait for 5.000 minute(s)  
214 Repeat from step 7, 5 times  
215 Empty RB1\_1to96 for 1 second(s)  
216 Wait for 4 second(s)  
217 Repeat from step 10, 25 times  
40 218 Empty RB1\_1to96 for 5.000 minute(s)  
219  
220 Dispense System Fluid Disdu1\_4\* 500ul to RB1\_1to96[1-96]  
221 Wait for 1.000 minute(s)  
222 Empty RB1\_1to96 for 1 second(s)  
45 223 Wait for 4 second(s)  
224 Repeat from step 17, 25 times  
225 Empty RB1\_1to96 for 5.000 minute(s)  
226

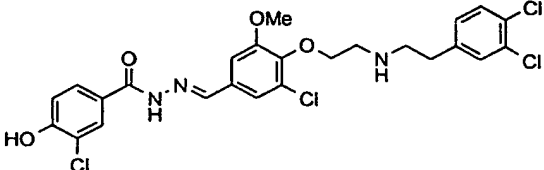
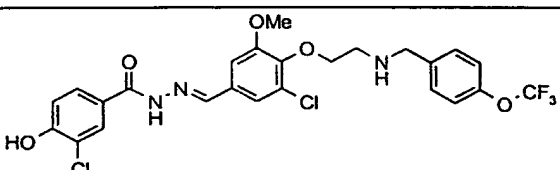
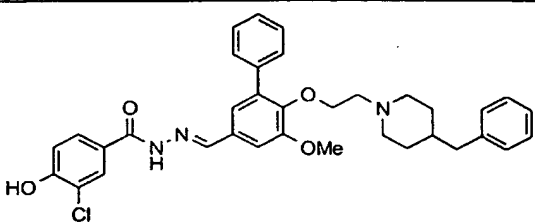
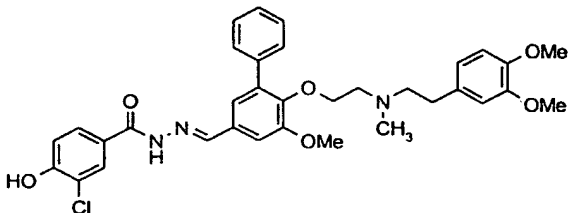
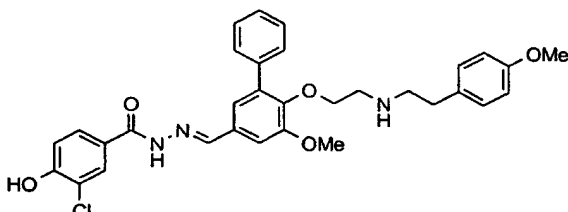
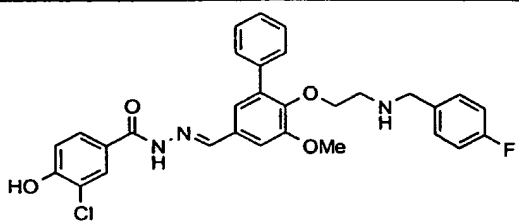
Dispense sequence files C:\ACT13\_28\R3-A.DSP, C:\ACT13\_28\R3-B.DSP, C:\ACT13\_28\R3-C.DSP and C:\ACT13\_28\R3-D.DSP are subroutines that control the combinatorial addition of the amines into the 4 reaction blocks each containing 96 wells in the synthesiser.

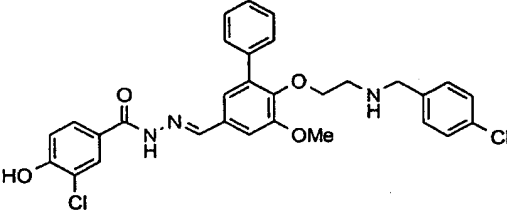
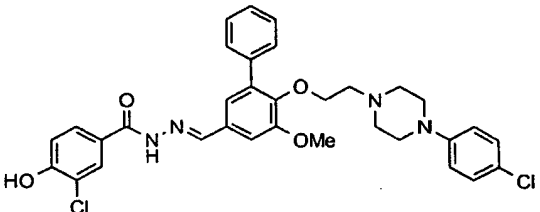
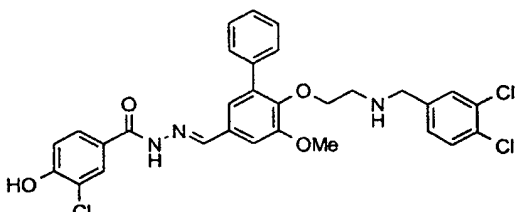
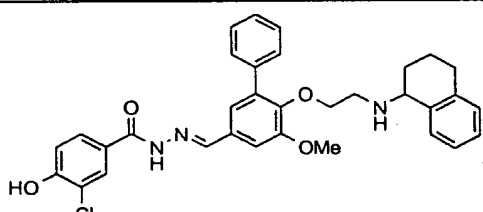
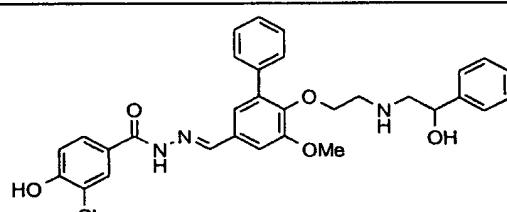
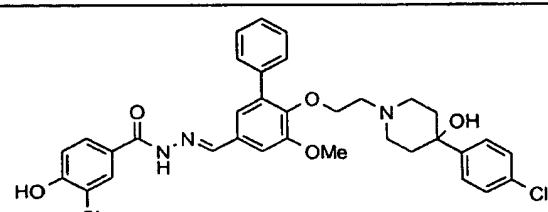
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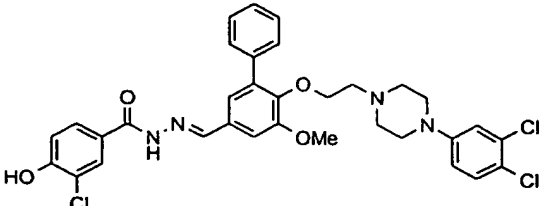
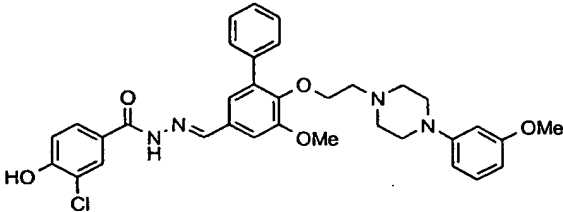
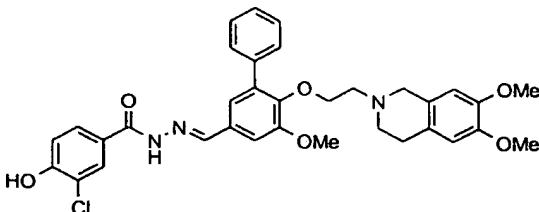
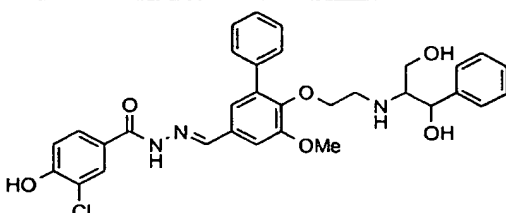
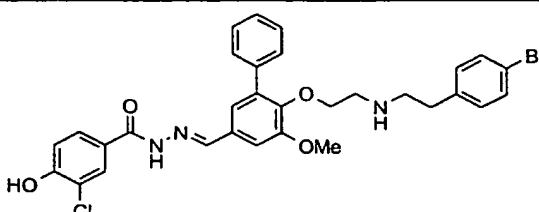
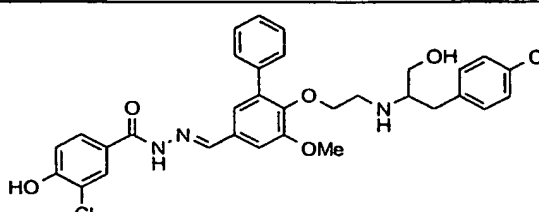
The library containing the following compounds was synthesized, and the products were characterised by HPLC-MS (molecular mass & retention time).

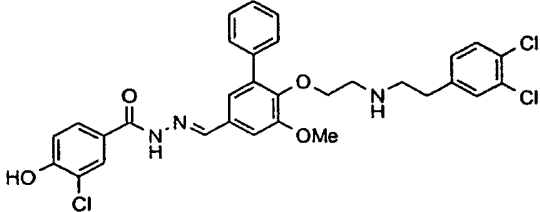
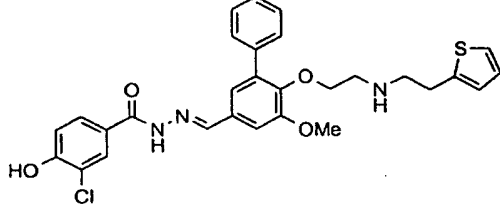
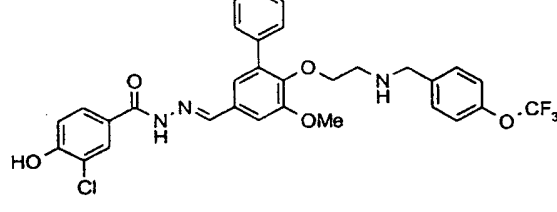
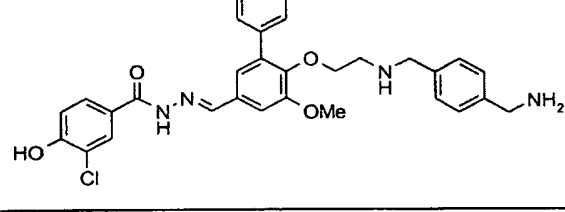
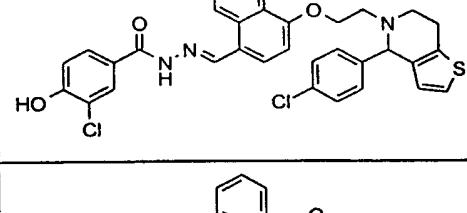
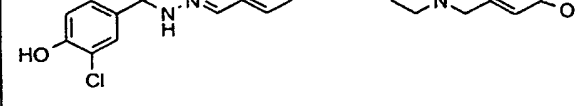
Ex No.	Structure	HPLC-MS (METHOD B) m/z	HPLC-MS (METHOD B) R <sub>t</sub> (minutes)
702		596	15.9
703		522	8.82
704		502	6.62
705		488	6.68
706		543	10.93
707		522	9.40
708		494	7.87

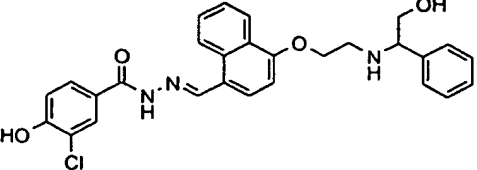
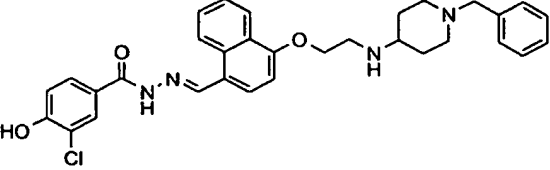
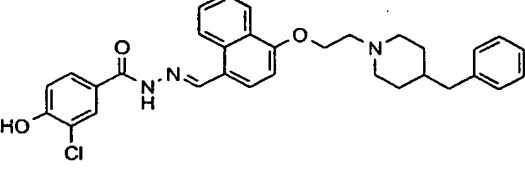
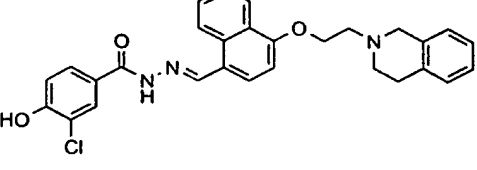
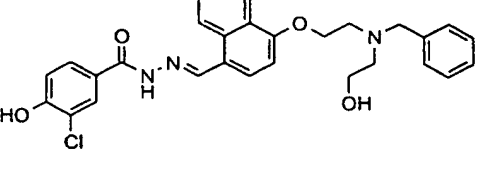
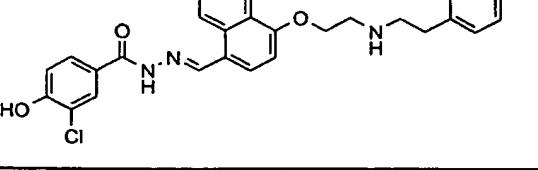
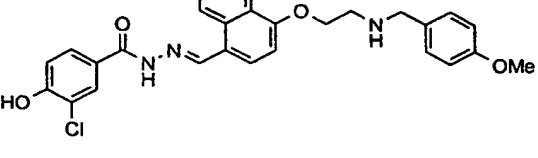
709		558	5.37
710		577	13.50
711		539	7.43
712		214	2.05
713		548	7.10
714		532	5.38
715		536	8.43
716		538	9.05

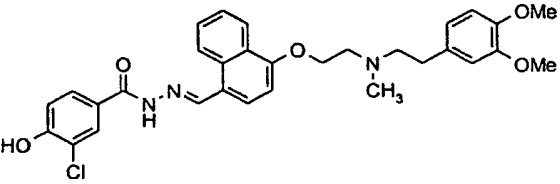
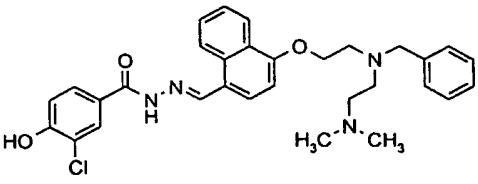
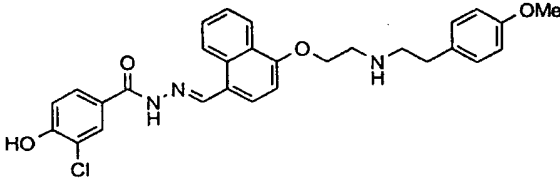
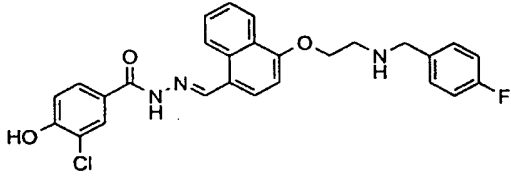
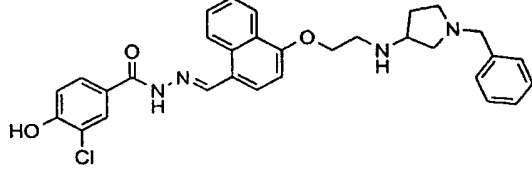
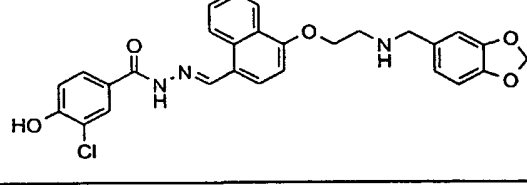
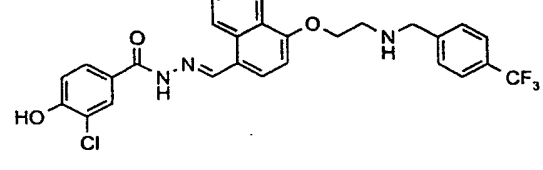
717		572	9.93
718		572	10.78
719		598	11.47
720		618	7.35
721		574	7.27
722		548	8.50

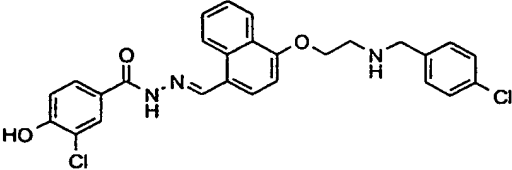
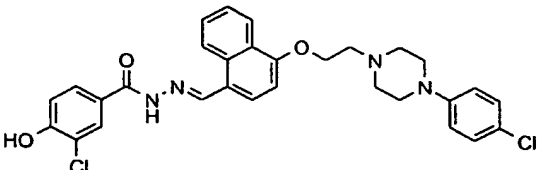
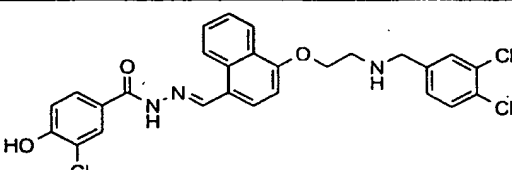
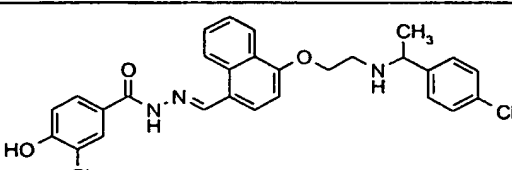
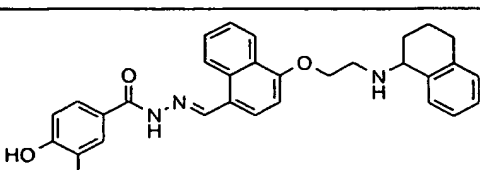
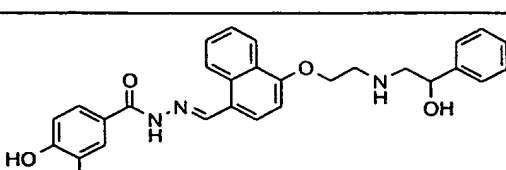
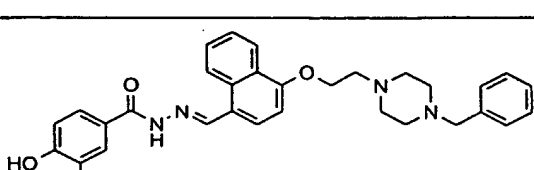
723		564	11.38
724		619	14.47
725		598	13.87
726		570	12.50
727		560	6.02
728		634	8.05

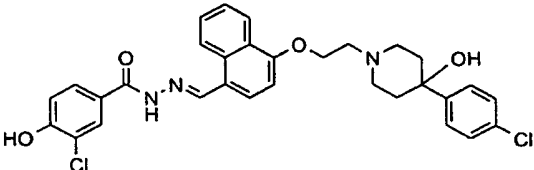
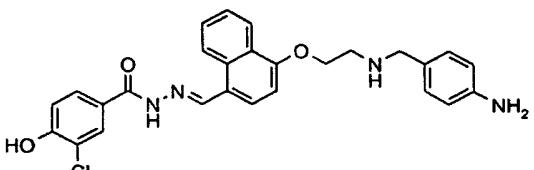
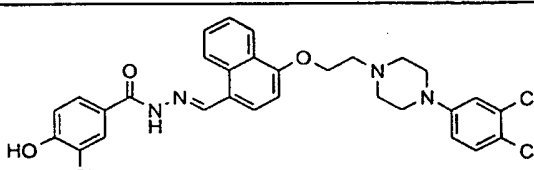
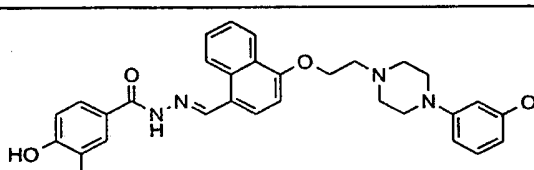
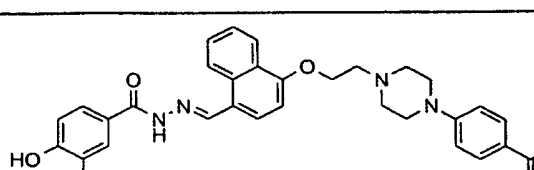
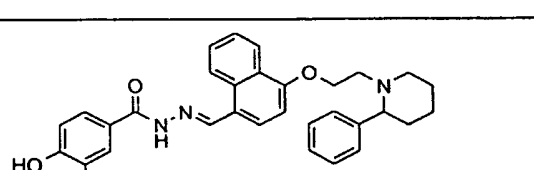
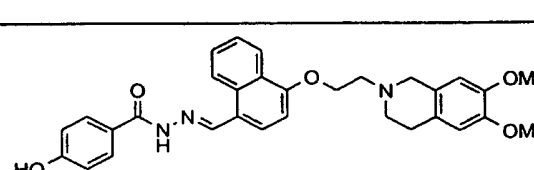
729		655	16.35
730		615	12.15
731		616	8.30
732		590	5.30
733		624	10.90
734		608	8.95

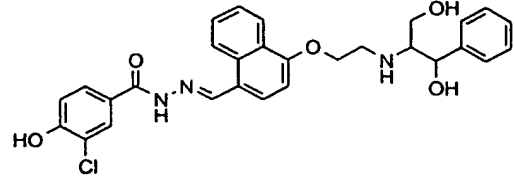
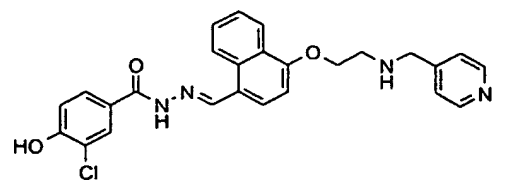
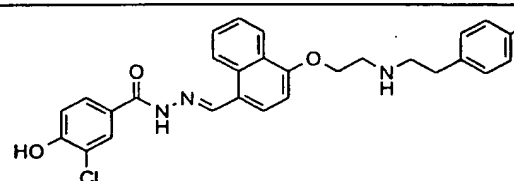
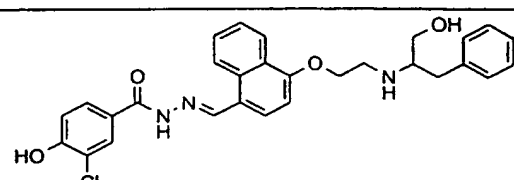
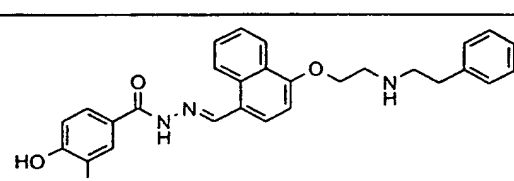
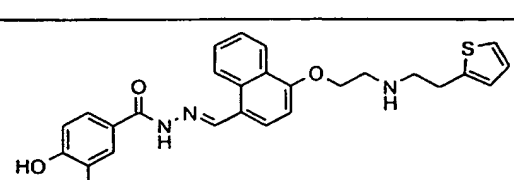
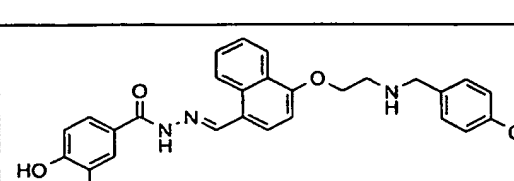
735		612	12.65
736		550	7.88
737		614	13.07
738		559	2.33
739		616	17.98
740		587	7.87

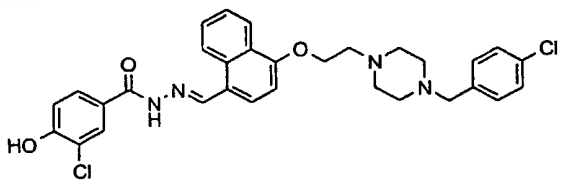
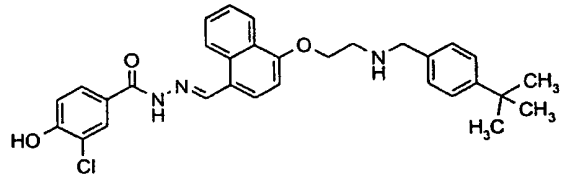
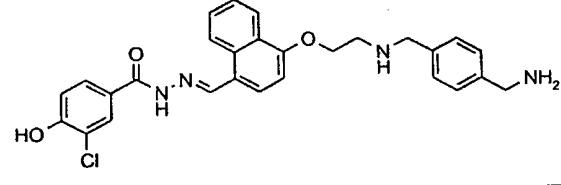
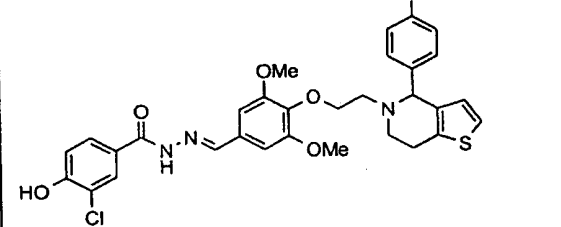
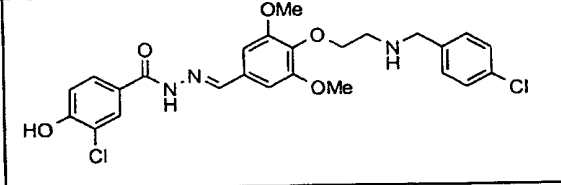
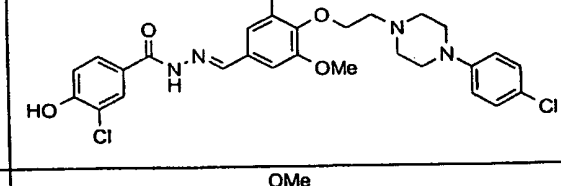
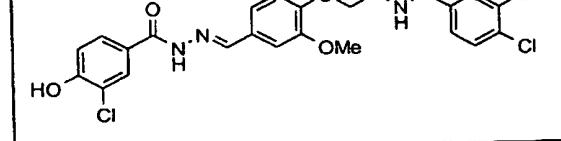
741		504	5.40
742		557	6.57
743		5.42	12.68
744		500	11.95
745		518	8.83
746		522	9.53
747		504	6.42

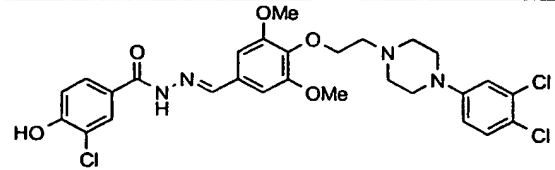
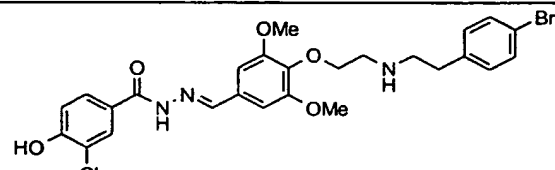
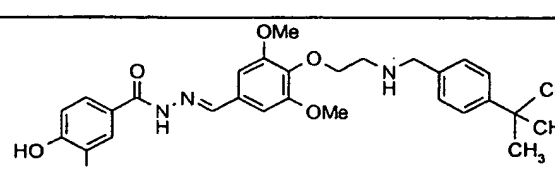
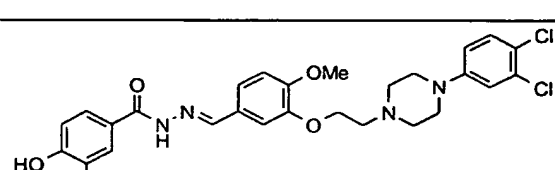
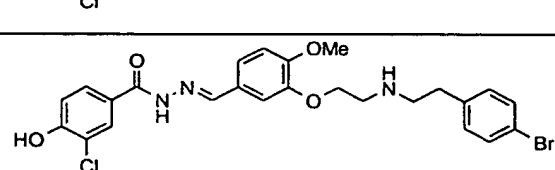
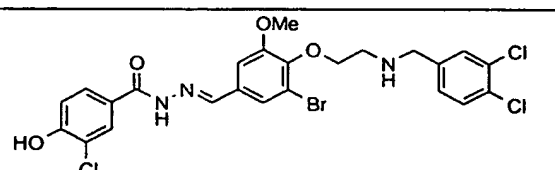
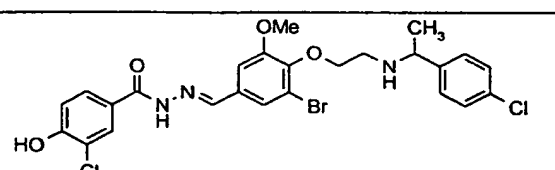
748		562	7.35
749		545	7.54
750		518	6.52
751		492	7.57
752		543	6.13
753		518	6.43
754		542	12.03

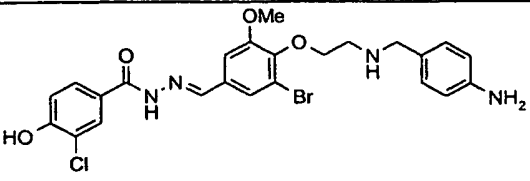
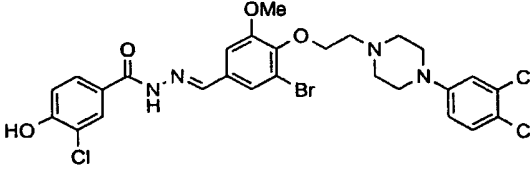
755		508	10.32
756		563	14.17
757		544	13.07
758		522	12.65
759		514	12.03
760		504	4.57
761		543	9.30

762		578	7.77
763		489	2.23
764		597	15.73
765		559	11.25
766		571	8.38
767		528	15.38
768		560	8.00

769		5.34	3.33
770		475	2.23
771		568	10.07
772		552	6.93
773		556	12.02
774		494	7.12
775		558	12.58

776		577	12.68
777		530	13.23
778		503	1.88
779		626	15.23
780		518	5.23
781		573	8.48
782		552	7.52

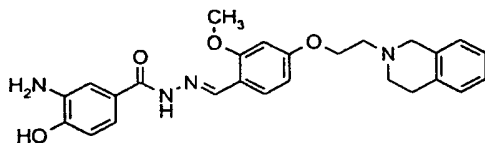
783		607	12.25
784		578	5.70
785		540	7.98
786		577	11.48
787		548	5.63
788		602	12.13
789		582	11.67

790		549	1.70
791		549	15.33

## EXAMPLE 792:

3-Amino-4-hydroxybenzoic acid 4-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)ethoxy]-2-methoxybenzylidene)hydrazide

5



The above 4-(2-bromoethoxy)-2-methoxybenzaldehyde (16.8 g, 65 mmol) ([building block 2]) was dissolved in acetone (300 ml) and potassium carbonate (44.9 g, 0.33 mol), potassium iodide (2 g) were added followed by addition of 1,2,3,4-tetrahydroisoquinoline (9.07 g, 72 mmol). The resulting mixture was stirred vigorously at reflux temperature for 16 hours. After cooling, the mixture was filtered and the inorganic precipitate was washed with acetone (100 ml). The combined acetone filtrates were concentrated in vacuo. The residue was dissolved in ethyl acetate (50 ml) and washed with water (2 x 20 ml) saturated sodium chloride (20 ml), dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue (23 g) was purified by column chromatography on silica gel (400 g) eluting first with a mixture of ethyl acetate and heptane (1:1, 2 liters) then with a mixture of ethyl acetate and heptane (2:1, 5 liters) to afford 12 g (60%) of 4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]-2-methoxybenzaldehyde as a solid. M.p.: 69 - 71 °C.

Calculated for C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>·0.25H<sub>2</sub>O: C, 72.24%; H, 6.86%; N, 4.43%.

Found: C, 72.79%; H, 6.86%; N, 4.46%; C, 72.65%; H, 6.88%; N, 4.47%.

Methyl 3-amino-4-hydroxybenzoate (5.0 g, 30 mmol) was dissolved in ethanol (50 ml) and hydrazine hydrate (4.4 ml, 90 mmol) was added and the resulting mixture was heated at re-  
flux temperature for 16 hours. After cooling the mixture was filtered and solid was washed  
with ethanol to afford after drying 1.4 g (28%) of 3-amino-4-hydroxybenzoic acid hydrazide  
as a solid. M.p.: 242 - 243 °C.

Calculated for  $C_7H_9N_3O_2$ : C, 50.30%; H, 5.43%; N, 25.14%.

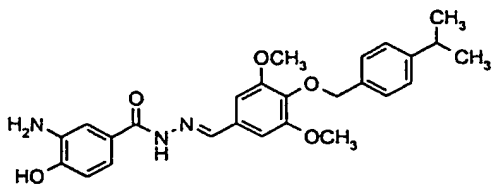
Found: C, 50.27%; H, 5.46%; N, 24.35%; C, 50.41%; H, 5.47%; N, 24.38%.

The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above 4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]-2-methoxybenzaldehyde (93 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16  
hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (2 x 4 ml) and dried by suction to afford 66 mg (48%) of the title compound as a solid. M.p.: 162 - 164 °C.

HPLC -MS (METHOD B):  $R_t$  = 6.50 minutes.  $m/z$  = 461.

#### EXAMPLE 793:

3-Amino-4-hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]-hydrazide



Syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde) (10.2 g, 55 mmol) was dissolved in DMF (45 ml), and 4-isopropylbenzylchloride (9.7 g, 55 mmol) and potassium carbonate (11.5 g) were added successively. The resulting mixture was heated at 60 °C for 16 hours. After cooling, the mixture was partitioned between water (150 ml) and ethyl acetate (3 x 100 ml).  
The combined organic extracts were washed with water (100 ml), saturated NaCl (100 ml),

dried (MgSO<sub>4</sub>), treated with activated carbon, filtered and concentrated in vacuo to afford 15 g (100%) of 4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzaldehyde as an oil.

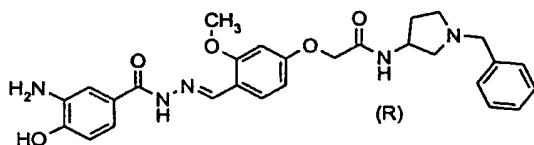
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> = 1.20 (9H, d), 2.89 (1H, h), 3.86 (6H, s), 4.98 (2H, s),  
5 7.23 (2H, d), 7.27 (2H, s), 7.36 (2H, d).

The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above 4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzaldehyde (93 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled  
10 mixture was filtered and the precipitate was washed with 2-propanol (2 x 4 ml) and dried by suction to afford 144 mg (100%) of the title compound as a solid. M.p.: 174 - 175 °C.

HPLC-MS (METHOD B): R<sub>t</sub> = 10.40 minutes. m/z = 464.

15 **EXAMPLE 794:**

(R)-2-{4-[(3-Amino-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenoxy}-N-(1-benzylpyrrolidin-3-yl)acetamide



20 (R)-(-)-1-Benzyl-3-aminopyrrolidine (5 g, 28 mmol) was dissolved in dichloromethane (10 ml). To this solution, a solution of bromoacetyl chloride (4.55 g, 28 mmol) in dichloromethane (5 ml) was added at room temperature. The mixture was stirred at room temperature for 16 hours. The mixture was filtered, washed with dichloromethane and dried in vacuo to afford 6.8 g (72%) of (3R)-N-(1-benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride as a solid  
25 which was used directly in the next step.

4-Hydroxy-2-methoxybenzaldehyde (2.05 g, 13 mmol) was dissolved in DMF (7 ml) and potassium carbonate (6.2 g, 45 mmol) was added followed by a suspension of the above (3R)-N-(1-Benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride (3.0 g, 9 mmol) in DMF (16  
30 ml). The resulting mixture was stirred at room temperature for 16 hours. The mixture was

then partitioned between water (100 ml) and ethyl acetate (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed with saturated sodium chloride (3 x 15 ml), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was crystallized from diethyl ether to afford 2.11 g (64%) (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide as a solid. M.p.: 98 - 101 °C.

Calculated for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4 \cdot 0.5\text{H}_2\text{O}$ :

C, 66.83%; H, 6.68%; N, 7.42%.

Found:

C, 67.15%; H, 6.57%; N, 7.75%;

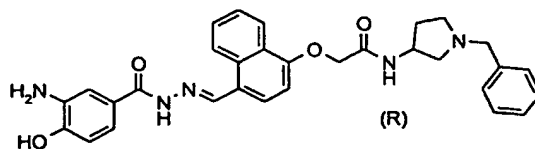
C, 66.96%; H, 6.57%; N, 7.77%.

The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (110 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (2 x 3 ml) and dried by suction to afford 109 mg (70%) of the title compound as a solid. M.p.: 157 - 160 °C.

HPLC-MS (METHOD B):  $R_t$  = 3.10 minutes.  $m/z$  = 518.

#### EXAMPLE 795:

(R)-2-[4-[(3-Amino-4-hydroxybenzoyl)hydrazonomethyl]naphthyl-1-yloxy]-N-(1-benzylpyrrolidin-3-yl)acetamide



4-Hydroxy-1-naphthaldehyde (2.32 g, 13 mmol) was dissolved in DMF (7 ml) and potassium carbonate (6.2 g, 45 mmol) was added followed by a suspension of the above (3R)-N-(1-Benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride (3.0 g, 9 mmol) in DMF (16 ml). The resulting mixture was stirred at room temperature for 16 hours. The mixture was then parti-

tioned between water (100 ml) and ethyl acetate (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed with saturated sodium chloride (3 x 15 ml), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (110 g) eluting with ethyl acetate to afford 1.7 g (49%) (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)acetamide as a solid.  
 5 M.p.: 105 - 107 °C.

Calculated for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_3 \cdot 0.25\text{H}_2\text{O}$ :

C, 73.36%; H, 6.28%; N, 7.13%.

10 Found:

C, 73.81%; H, 6.22%; N, 7.11%;

C, 73.92%; H, 6.23%; N, 7.11%.

The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)acetamide (116 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (6 x 2 ml) and dried by suction to afford 140 mg (87%) of the title compound as a solid. M.p.: 187 - 192 °C.

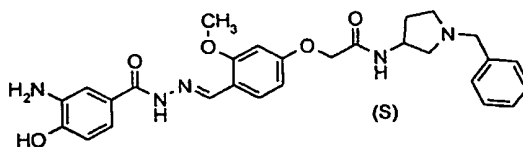
20

HPLC-MS (METHOD B):  $R_t$  = 5.72 minutes.  $m/z$  = 538.

#### EXAMPLE 796:

(S)-2-[4-[(3-Amino-4-hydroxybenzoyl)-hydrazonomethyl]-3-methoxyphenoxy]-N-(1-benzylpyrrolidin-3-yl)acetamide

25



(S)-(+)-1-Benzyl-3-aminopyrrolidine (6 g, 34 mmol) was dissolved in dichloromethane (12 ml). To this solution, a solution of bromoacetyl chloride (5.46 g, 34 mmol) in dichloromethane

30

(5 ml) was added at room temperature. The mixture was stirred at room temperature for 16 hours. The mixture was filtered, washed with dichloromethane and dried *in vacuo* to afford 7.3 g (64%) of (3S)-N-(1-benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride as a solid which was used directly in the next step.

5

4-Hydroxy-2-methoxybenzaldehyde (2.39 g, 16 mmol) was dissolved in DMF (10 ml) and potassium carbonate (7.3 g, 52 mmol) was added followed by a suspension of the above (3S)-N-(1-benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride (3.5 g, 10 mmol) in DMF (20 ml). The resulting mixture was stirred at room temperature for 16 hours. The mixture was then partitioned between water (100 ml) and ethyl acetate (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed with saturated sodium chloride (3 x 15 ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue (4 g) was crystallised from a mixture of diethyl ether and heptane, filtered and dried *in vacuo* to afford 2.7 g (71%) (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)-acetamide as a solid. M.p.: 96 - 100 °C.

15

Calculated for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>·0.25H<sub>2</sub>O:

C, 67.63%; H, 6.62%; N, 7.51%.

Found:

20 C, 67.35%; H, 6.61%; N, 7.85%;

C, 67.24%; H, 6.59%; N, 7.82%.

25

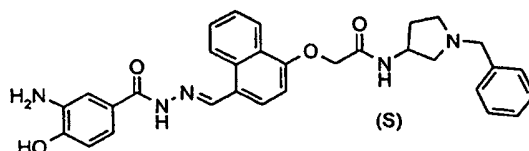
The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (110 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (6 x 2 ml) and dried by suction to afford 109 mg (70%) of the title compound as a solid. M.p.: 139 - 141 °C.

30

HPLC-MS (METHOD B): R<sub>t</sub> = 3.15 minutes. m/z = 518.

EXAMPLE 797:

(S)-2-{4-[(3-Amino-4-hydroxybenzoyl)hydrazonomethyl]naphthyl-1-yloxy}-N-(1-benzylpyrrolidin-3-yl)acetamide



4-Hydroxy-1-naphthaldehyde (2.71 g, 16 mmol) was dissolved in DMF (10 ml) and potassium carbonate (7.25 g, 52 mmol) was added followed by a suspension of the above (3S)-N-(1-benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride (3.0 g, 10 mmol) in DMF (20 ml). The resulting mixture was stirred at room temperature for 16 hours. The mixture was then partitioned between water (100 ml) and ethyl acetate (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed with saturated sodium chloride (3 x 15 ml), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue (4 g) was purified by column chromatography on silica gel (110 g) eluting with ethyl acetate to give an oil (2 g), which was crystallized from a mixture of diethyl ether and heptane to afford 1.8 g (45%) (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)-acetamide as a solid. M.p.: 96 - 97 °C.

15

Calculated for  $C_{24}H_{24}N_2O_3 \cdot 0.25H_2O$ :

C, 73.36%; H, 6.28%; N, 7.13%.

**Found:**

C, 73.58%; H, 6.28%; N, 7.05%;

20 C, 73.55%; H, 6.27%; N, 7.03%.

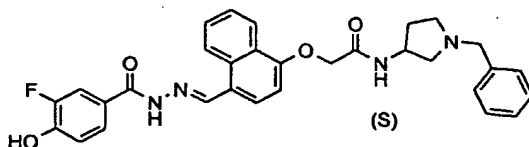
The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)acetamide (116 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (3 x 3 ml) and dried by suction to afford 143 mg (89%) of the title compound as a solid. M.p.: 192 - 193 °C.

HPLC-MS (METHOD B): Rt = 5.18 minutes. m/z = 538.

30

## EXAMPLE 798:

(S)-2-(4-[(3-Fluoro-4-hydroxybenzoyl)hydrazonomethyl]naphthyl-1-yloxy)-N-(1-benzylpyrrolidin-3-yl)acetamide



5 This compound was prepared on solid phase using resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide, prepared similarly as described above for the resin bound 3-chloro-4-hydroxybenzoic acid hydrazide. Thus, methyl 3-fluoro-4-hydroxybenzoate was attached to the resin. Hydrolysis of the methyl ester (aq. LiOH, dioxane, 60 °C) followed by reaction with hydrazine (PyBOP, hydrazine, DMF) afforded resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide.

The resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) was swelled in DMF (10 ml) for 30 minutes and filtered. This was repeated once more. DMF (4 ml) and the above (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)acetamide (0.4 g, 0.94 mmol) were added followed by triethyl orthoformate (1.5 ml) and the resulting mixture was shaken at room temperature for 16 hours. The mixture was filtered and the resin was successively washed with DMF (5 x 4 ml) and dichloromethane (5 x 4 ml). The compound was cleaved off the resin by addition of 50% TFA in dichloromethane (6 ml) and shaking at room temperature for 1 hour. Filtration followed by extraction of the resin with a mixture of methanol and dichloromethane (4:6) (2 x 4 ml) followed by extraction with dichloromethane (4 ml). The combined filtrates were concentrated in vacuo, stripped successively with wet methanol, dichloromethane, methanol and dichloromethane. The residue (0.39 g) was purified by column chromatography on silica gel (40 g) eluting first with a mixture of dichloromethane, ethanol and 25% aq. ammonia (90:9:1), then with (85:13.5:1.5) and finally with (80:18:2).

25 Pure fractions were pooled and concentrated in vacuo to afford 0.15 g of the title compound.

HPLC-MS (METHOD B):  $R_t$  = 8.82 minutes.  $m/z$  = 541.

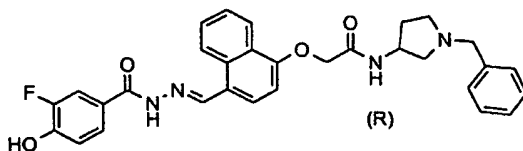
Calculated for  $C_{31}H_{29}N_4O_4F \cdot 0.25CH_2Cl_2$ :

30 C, 66.81%; H, 5.29%; N, 9.97%. Found: C, 67.30%; H, 5.48%; N, 10.03%;

C, 67.33%; H, 5.49%; N, 10.02%.

EXAMPLE 799:

(R)-2-[4-[(3-Fluoro-4-hydroxybenzoyl)hydrazonomethyl]naphthyl-1-yloxy]-N-(1-benzylpyrrolidin-3-yl)acetamide



This compound was prepared similarly as described in the previous example starting from resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) and the above (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)acetamide (0.4 g, 0.94 mmol). After cleavage the compound was purified by column chromatography to afford 0.14 g of the title compound.

HPLC-MS (METHOD B):  $R_t$  = 9.02 minutes.  $m/z$  = 541.

Calculated for  $C_{31}H_{29}N_4O_4F \cdot 0.25CH_2Cl_2$ :

C, 66.81%; H, 5.29%; N, 9.97%.

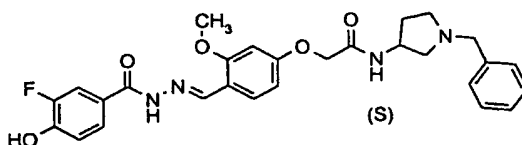
Found:

C, 66.77%; H, 5.46%; N, 10.02%;

C, 67.14%; H, 5.42%; N, 9.97%.

EXAMPLE 800:

(S)-2-[4-[(3-Fluoro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenoxy]-N-(1-benzylpyrrolidin-3-yl)acetamide



This compound was prepared similarly as described in the previous example starting from resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) and the above (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (0.4 g, 0.94 mmol). After

cleavage the compound was purified by column chromatography to afford 0.13 g of the title compound.

HPLC-MS (METHOD B):  $R_t$  = 3.68 minutes.  $m/z$  = 521.

5

Calculated for  $C_{28}H_{29}N_4O_5F \cdot 0.25CH_2Cl_2$ :

C, 62.63%; H, 5.49%; N, 10.34%.

Found:

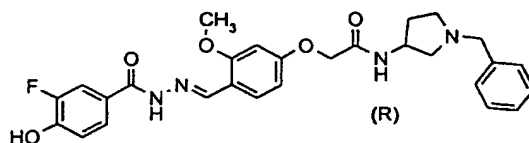
C, 62.92%; H, 5.83%; N, 10.15%;

10 

C, 62.71%; H, 5.81%; N, 10.16%.

EXAMPLE 801:

(R)-2-{4-[(3-Fluoro-4-hydroxybenzoyl)-hydrazonomethyl]-3-methoxyphenoxy}-N-(1-benzylpyrrolidin-3-yl)acetamide



15

This compound was prepared similarly as described in the previous example starting from resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) and the above (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (0.4 g, 0.94 mmol). After cleavage the compound was purified by column chromatography to afford 0.16 g of the title compound.

20

HPLC-MS (METHOD B):  $R_t$  = 4.18 minutes.  $m/z$  = 521.

Calculated for  $C_{28}H_{29}N_4O_5F \cdot 0.25CH_2Cl_2$ :

25 

C, 62.63%; H, 5.49%; N, 10.34%.

Found:

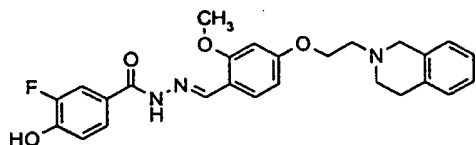
C, 62.65%; H, 5.73%; N, 10.31%;

C, 62.84%; H, 5.81%; N, 10.30%.

30 

EXAMPLE 802:

3-Fluoro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)ethoxy]-2-methoxybenzylidene}hydrazide



This compound was prepared similarly as described in the previous example starting from  
5 resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) and the above 4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]-2-methoxybenzaldehyde (0.4 g, 0.94 mmol). After cleavage the compound was purified by column chromatography to afford 0.13 g of the title compound.

10 HPLC-MS (METHOD B):  $R_t$  = 7.60 minutes.  $m/z$  = 464.

Calculated for  $C_{26}H_{26}N_3O_4F \cdot 0.5CH_2Cl_2$ :

C, 62.91%; H, 5.38%; N, 8.30%.

Found:

15 C, 62.68%; H, 5.47%; N, 8.02%;

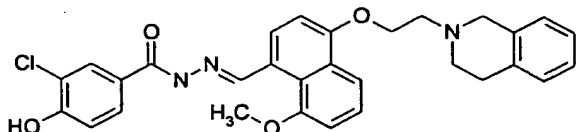
C, 62.48%; H, 5.43%; N, 8.01%.

The HPLC-MS (METHOD A) analyses were performed on a PE Sciex API 100 LC/MS Sys-  
tem using a Waters<sup>TM</sup> 3 mm x 150 mm 3.5  $\mu$  C-18 Symmetry column and positive ionspray  
20 with a flow rate of 20  $\mu$ L/minute. The column was eluted with a linear gradient of 5-90% A,  
85-0% B and 10% C in 15 minutes at a flow rate of 1 ml/min (solvent A = acetonitrile, solvent  
B = water and solvent C = 0.1% trifluoroacetic acid in water).

The HPLC-MS (METHOD B) analyses were performed on a system identical to the one de-  
scribed above, the only difference being the eluent. The column was eluted with a linear gra-  
25 dient of 30-80% A, 60-10% B and 10% D in 15 minutes at a flow rate of 1 ml/min (solvent A  
= acetonitrile, solvent B = water and solvent D = 20 mM ammonium acetate in water, pH 7).

EXAMPLE 803:

3-Chloro-4-hydroxy-benzoic acid {4-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)-ethoxy]-8-methoxy-naphthalen-1-ylmethylene}-hydrazide



- 5 4-hydroxy-8-methoxynaphthalene-1-carbaldehyde (1 g, 5 mmol) was dissolved in DMF (15 mL). To this mixture potassium carbonate (3.4 g, 25 mmol) and 1,2-dibromoethane (4 mL, 50 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. Water (150 mL) was added and the resulting mixture was extracted with ethyl acetate (3 x 90 mL). The combined organic extracts were washed with saturated sodium chloride  
10 (100 mL), dried (MgSO<sub>4</sub>) and evaporated in vacuo to afford 1.13 g (74%) of 4-(2-bromoethoxy)-8-methoxynaphthalene-1-carbaldehyde.

HPLC-MS (Method A): R<sub>t</sub> = 14.1 minutes. m/z = 309.

- 15 <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> = 3.99 (3H, s), 7.00 (1H, d), 7.20 (1H, d), 7.47 (1H, t), 7.88 (2H, m), 10.9 (1H, s).

- The above resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (2 g, 1.8 mmol) was swelled in DMF (25 mL) for 30 minutes and the above 4-(2-bromoethoxy)-8-methoxynaphthalene-1-carbaldehyde (1.7 g, 5.4 mmol) was added followed by triethyl orthoformate (1.2 mL) and the resulting mixture was shaken at room temperature for 16 hours. The mixture was filtered and the resin was successively washed with DMF (3 x 25 mL), dichloromethane (4 x 25 mL) and N-methyl pyrrolidin-2-one (NMP) (2 x 25 mL). NMP (25 mL) was added followed by potassium iodide (0.6 g) and 1,2,3,4-tetrahydro-isoquinoline  
25 (2.25 mL, 18 mmol) and the resulting mixture was shaken at room temperature for 16 hours. The mixture was filtered and the resin was successively washed with NMP (2 x 25 mL) and dichloromethane (6 x 25 mL). The compound was cleaved off the resin by addition of 50% TFA in dichloromethane (30 mL) and shaking at room temperature for 1 hour. After filtration followed by extraction of the resin with dichloromethane (2 x 30 mL) the combined filtrates  
30 were concentrated in vacuo. The residue was partitioned between ethyl acetate (80 mL) and saturated sodium hydrogen carbonate (100 mL). The aqueous phase was extracted with

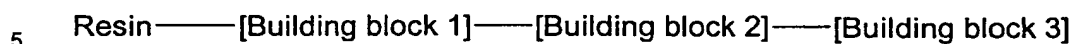
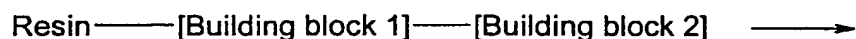
ethyl acetate (2 x 80 mL) and the combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (200 mL) eluting with a mixture of dichloromethane and methanol (9:1). This afforded 217 mg of the title compound.

5

HPLC-MS (Method A):  $R_t$  = 9.14 minutes.  $m/z$  = 530.

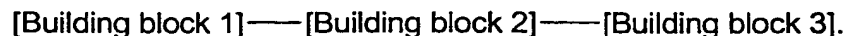
General Procedure for Examples 804 to 824:

The compounds were prepared as single entities according to the following equation



and were simultaneously deprotected (when required) and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

10



15

The following compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1] and attachment of [Building block 2] was done manually, whereas the attachment of [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 496 HTS in several runs.

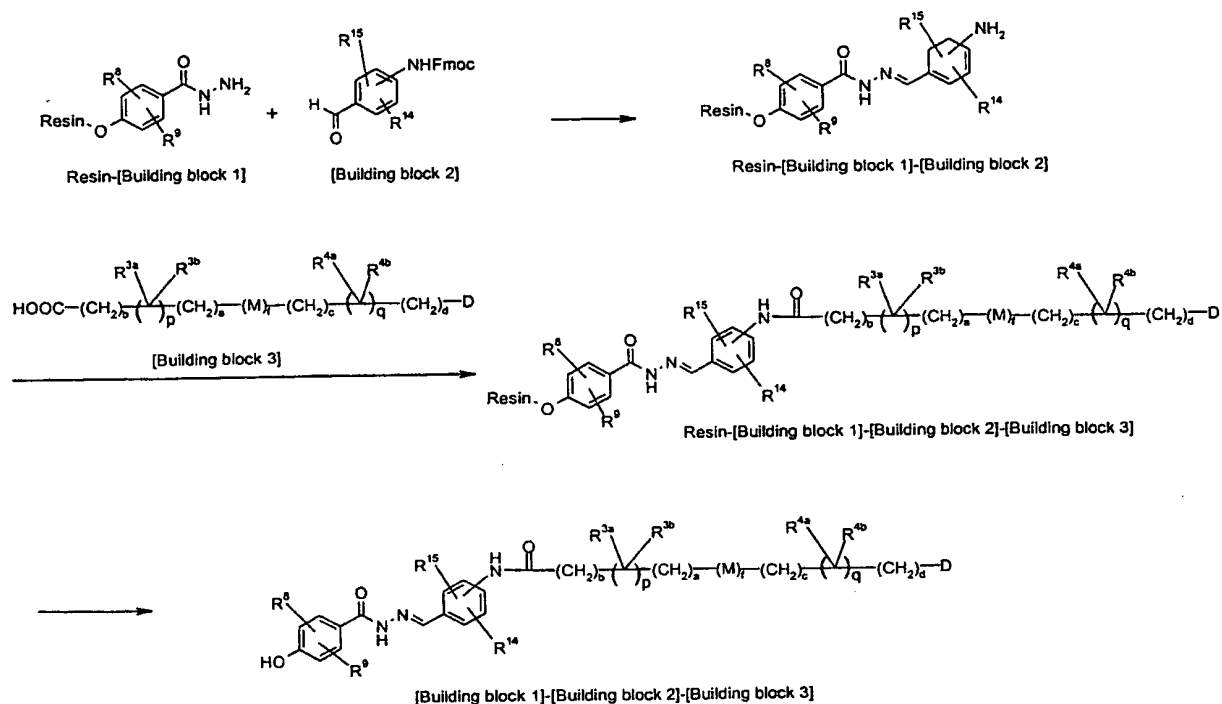
The starting resin, Resin-[Building block 1], was prepared as described above.

20

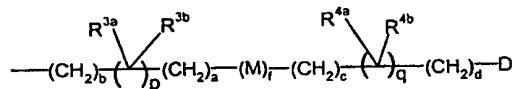
The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

25

All compounds are based on successive attachment of [Building block 2] and [Building block 3] to Resin-[Building block 1] in a combinatorial way according to the following formulae, which are included in the general formula II:

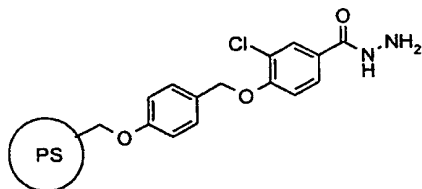


wherein  $R^8$ ,  $R^9$ ,  $R^{14}$ ,  $R^{15}$  and

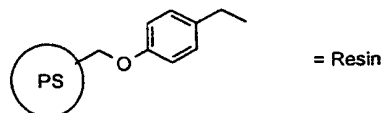


5 are as defined for formula I.

The following resin, here depicted as Resin-[Building block 1] was used:

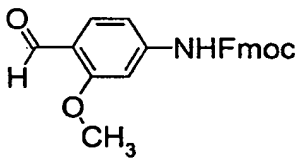
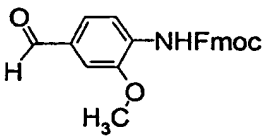
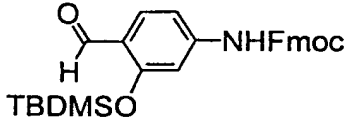
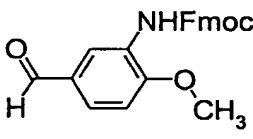


where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:

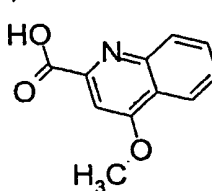
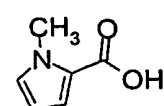
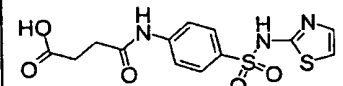
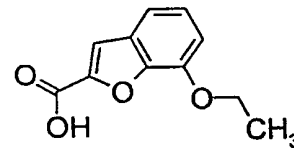
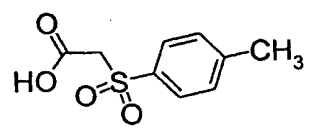
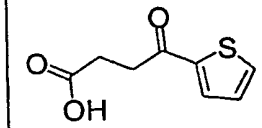
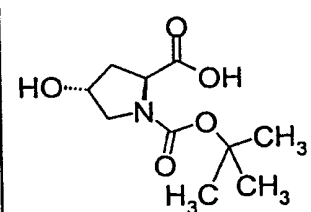
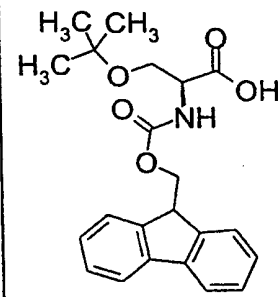
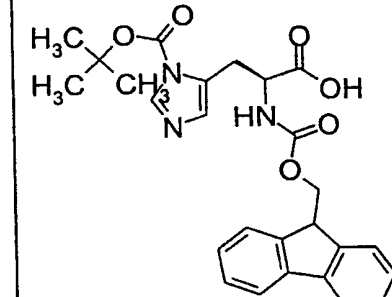


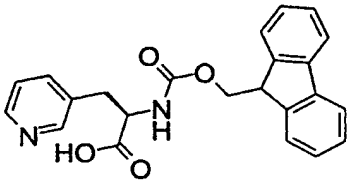
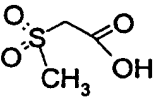
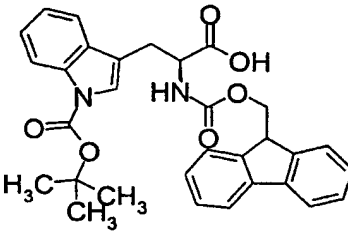
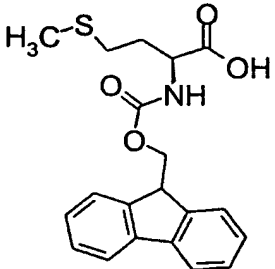
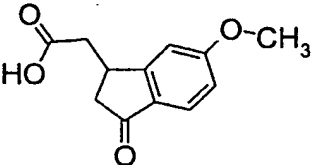
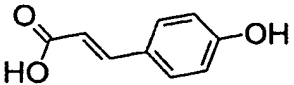
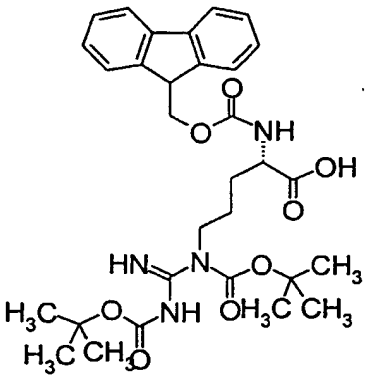
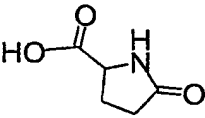
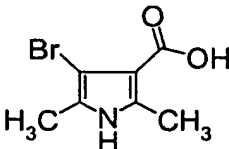
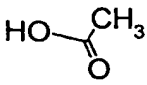
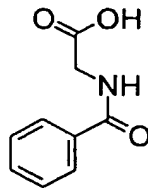
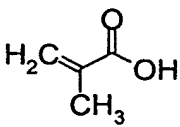
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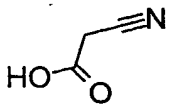
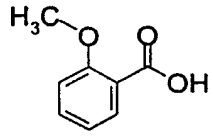
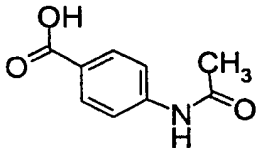
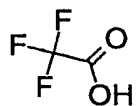
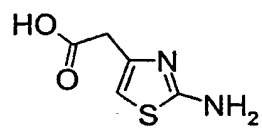
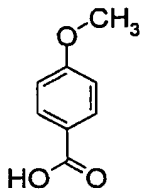
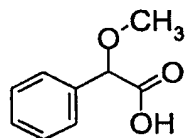
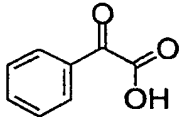
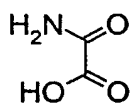
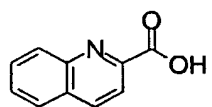
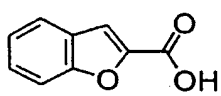
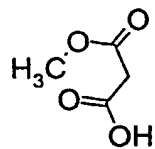
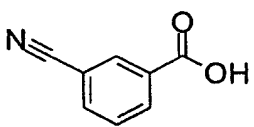
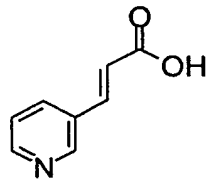
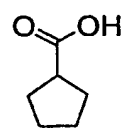
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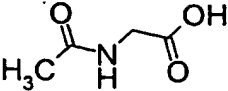
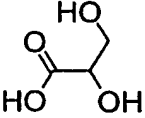
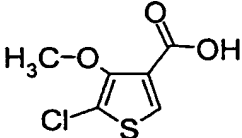
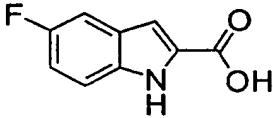
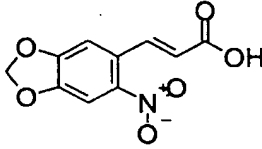
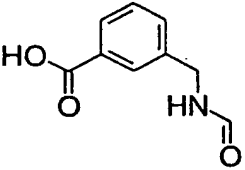
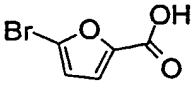
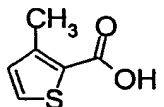
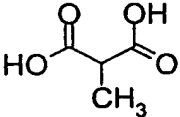
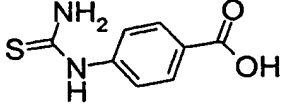
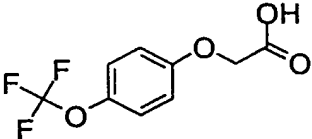
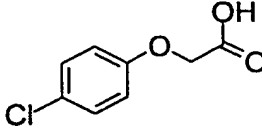
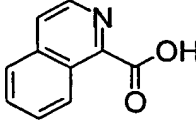
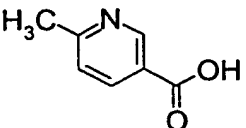
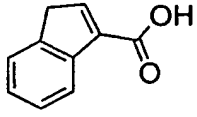
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<p>3-(tert-Butyldimethylsilyloxy)-4- formylphenyl)carbamic acid 9H-fluoren-9- ylmethyl ester:</p> 	<p>(5-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:</p> 

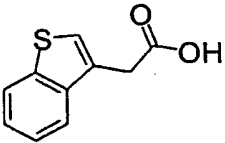
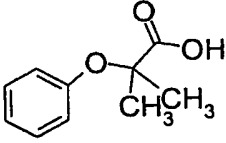
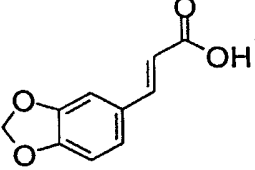
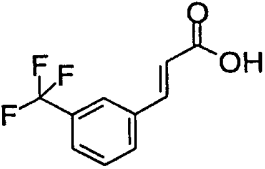
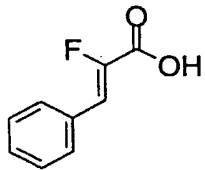
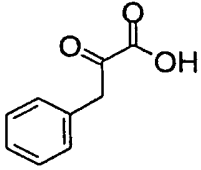
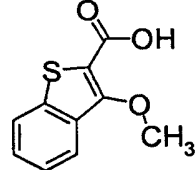
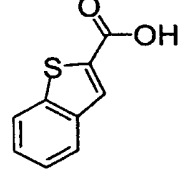
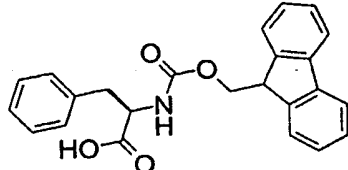
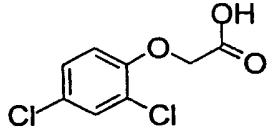
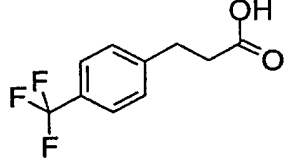
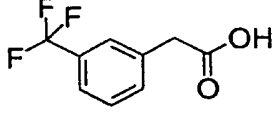
[Building block 3]:

<p>4-Methoxy-2-quinolinecarboxylic acid</p>  <chem>COc1cc(C(=O)O)cnc2ccccc12</chem>	<p>N-Methylpyrrole-2-carboxylic acid</p>  <chem>CC1=CNC(=O)O1</chem>	<p>Succinylsulfathiazole</p>  <chem>OC(=O)CCC(=O)Nc1ccc(S(=O)(=O)Nc2ccsc2)cc1</chem>
<p>7-Ethoxybenzofuran-2-carboxylic acid</p>  <chem>CCOC1=CC=C2C(=C1)OC(=C2)C(=O)O</chem>	<p>4-Toluenesulfonylacetic acid</p>  <chem>CC(=O)OS(=O)(=O)c1ccc(C)cc1</chem>	<p>3-(2-Thienoyl)propionic acid</p>  <chem>OC(=O)CCC(=O)c1ccsc1</chem>
<p>Boc-Hyp-OH</p>  <chem>CC(C)(C)OC(=O)N1CCC(O)C1C(=O)O</chem>	<p>N-fmoc-O-t-butyl-L-serine</p>  <chem>CC(C)(C)OC(=O)N[C@@H](Cc1c2ccccc2c3ccccc13)C[C@@H](C(=O)O)CO</chem>	<p>Fmoc-His(Boc)-OH</p>  <chem>CC(C)(C)OC(=O)N[C@@H](Cc1c2ccccc2c3ccccc13)C[C@@H](Cc4c[nH]c5c(c4)C(=O)OC(=O)N5C(=O)O)C</chem>

<p>Foc-beta-(3-pyridyl)-D-Ala-OH</p> 	<p>Methanesulfonylacetic acid</p> 	<p>Fmoc-Trp(Boc)-OH</p> 
<p>Fmoc-L-Methionine</p> 	<p>5-Methoxy-1-indanone-3-acetic acid</p> 	<p>4-Hydroxycinnamic acid</p> 
<p>Fmoc-Arg(Boc)-2-OH</p> 	<p>5-Oxopyrrolidine-2-carboxylic acid</p> 	<p>4-Bromo-2,5-dimethyl-1-H-pyrrole-3-carboxylic acid</p> 
<p>Acetic acid</p> 	<p>Hippuric acid</p> 	<p>2-Methylpropenoic acid</p> 

<p>Cyano-acetic acid</p> 	<p>O-Anisic acid</p> 	<p>4-Acetamidobenzoic acid</p> 
<p>Trifluoroacetic acid</p> 	<p>2-Amino-4-thiazole acetic acid</p> 	<p>p-Anisic acid</p> 
<p>Alfa-Methoxyphenylacetic acid</p> 	<p>Benzoylformic acid</p> 	<p>Oxamic acid</p> 
<p>Quinolin-2-carboxylic acid</p> 	<p>Benzofuran-2-carboxylic acid</p> 	<p>Monomethyl malonate</p> 
<p>3-Cyanobenzoic acid</p> 	<p>3-(3-Pyridyl)acrylic acid</p> 	<p>Cyclopentanecarboxylic acid</p> 

<p>N-Acetylglycine</p> 	<p>DL-Glyceric acid</p> 	<p>2-Chloro-3-methoxythiophene-4-carboxylic acid</p> 
<p>5-Fluoroindole-2-carboxylic Acid</p> 	<p>3-(4,5-Methylenedioxy-2-nitrophenyl)acrylic acid</p> 	<p>3-(Formylaminomethyl)benzoic acid</p> 
<p>5-Bromo-2-furoic Acid</p> 	<p>3-Methylthiophene-2-carboxylic acid</p> 	<p>Methylmalonic acid</p> 
<p>4-Thioureido-benzoic acid</p> 	<p>(4-Trifluoromethoxy)phenoxy acetic acid</p> 	<p>(4-Chlorophenoxy)acetic acid</p> 
<p>Isoquinoline-1-carboxylic acid</p> 	<p>6-Methylnicotinic acid</p> 	<p>3H-Indene-1-carboxylic acid</p> 

Benzo[b]thien-3-yl acetic acid 	2-methyl-2-phenoxypropionic acid 	3-Benzo[1,3]dioxol-5-yl-acrylic acid 
3-(3-Trifluoromethylphenyl) acrylic acid 	2-Fluoro-3-phenylacrylic acid 	2-Oxo-3-phenylpropionic acid 
3-Methoxybenzo[b]thiophene-2-carboxylic acid 	Benzo[b]thiophene-2-carboxylic acid 	Fmoc-phenylalanine 
(2,4-Dichlorophenoxy)acetic acid 	3-(4-Trifluoromethylphenyl)-propionic acid 	(3-Trifluoromethylphenyl)-acetic acid 

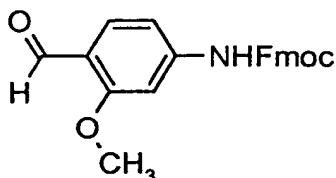
Preparation of resin-[Building block 1]:

5

This resin was prepared as described above.

Preparation of [Building block 2]:

(4-Formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



- 5 Methyl 4-amino-2-methoxybenzoate (14.7 g, 7.3 mmol) and Fmoc-Osu (26.1 g, 77.3 mmol) were stirred in a mixture of acetonitrile and water (1:1, 320 mL) at reflux for 16 hr. The reaction mixture was concentrated to half the volume and the precipitate isolated by filtration. The isolated solid was dissolved in ethyl acetate (300 mL) and washed with 0.4 N hydrochloric acid (200 mL), 0.2 N hydrochloric acid (200 mL), water (200 mL) and a 20 % saturated solution of sodium chloride (200 mL). After drying (magnesium sulphate) the organic phase was concentrated in vacuo, and the solid residue was washed with methanol and dried.

- The crude product (12g) was dissolved in dichloromethane (1 L) under nitrogen and a solution of diisobutylaluminium hydride (90 mL, 1.2 M in toluene) was dropwise added at 0-5°C.
- 15 The reaction mixture was stirred at 20°C for 16 hr and quenched by dropwise addition of water (58 mL) at 0-5 °C. The reaction mixture was stirred at 20°C for 3 hr and filtered. The filtrate was concentrated in vacuo. The crude product (6.8 g) was suspended in dichloromethane (400 mL) and manganese dioxide (15.6 g, 180 mmol) was added. The mixture was stirred for 16 hr at 20°C and filtered. The filtrate was concentrated in vacuo to give
- 20 5.1 g of the title compound.

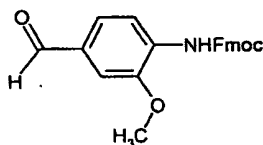
m.p. 187-188°C

HPLC-MS (METHOD A):  $R_t$  = 15.1 min,  $m/z$  = 374.

Micro analysis: calculated: C, 73.98; H, 5.13; N, 3.75%

25 found: C, 73.44; H, 5.20; N, 3.56%

(4-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



Thionylchloride (12.8 g, 108 mmol) was dropwise added to an ice cold suspension of 4-amino-3-methoxybenzoic acid (12.3 g, 72 mmol) in methanol (250 mL). The reaction mixture was stirred at 20°C for 16 hr and concentrated in vacuo. Ethyl acetate (250 mL) and a saturated solution of sodium hydrogen carbonate (150 mL) were added and the organic phase was washed with saturated solutions of sodium hydrogen carbonate (2x50 mL), dried (magnesium sulphate) and concentrated in vacuo. The crude product (12.5 g) and Fmoc-Osu (28 g, 83 mmol) was stirred in a mixture of acetonitrile and water (1:1, 240 mL) at 90°C for 16 hr. The reaction mixture was concentrated to half the volume. Ethyl acetate (200 mL) was added together with 0.4N hydrochloric acid (150 mL). The organic phase was washed with 0.2N hydrochloric acid (100 mL), water (100 mL) and a saturated solution of sodium chloride (2x100 mL). After drying (magnesium sulphate) the organic phase was concentrated in vacuo, and the residue was crystallized from methanol and dried.

m.p. 96-98°C

HPLC (Method 1)  $R_t$  = 32.4 min

Micro analysis: calculated: C, 71.45; H, 5.25; N, 3.47%

found: C, 71.32; H, 5.24; N, 3.41%

20

The product (12 g, 29.7 mmol) was dissolved in dichloromethane (800 mL) under nitrogen and a solution of diisobutylaluminium hydride (90 mL, 1.2M in toluene) was dropwise added at 0-5°C. The reaction mixture was stirred at 20°C for 16 hr and quenched by dropwise addition of water (58 mL) at 0-5°C. The reaction mixture was stirred at 20°C for 3 hr and filtered. The filtrate was concentrated in vacuo to give 5.5 g of product (m.p. 169-171°C). The product (5.5 g) was suspended in dichloromethane (325 mL) and manganese dioxide (12.8 g, 148 mmol) was added. The mixture was stirred for 16 hr at 20°C and filtered. The filtrate was concentrated in vacuo to give 3.5 g of the title compound. Recrystallization from ethyl acetate.

30

m.p. 150-152°C

HPLC (Method 1)  $R_t$  = 30.6 min

Micro analysis: calculated: C, 73.98; H, 5.13; N, 3.75%

5 found: C, 73.54; H, 5.18; N, 3.65%

3-(tert-Butyldimethylsilyloxy)-4-formylphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



4-(9H-Fluoren-9-ylmethoxycarbonylamino)-2-hydroxybenzoic acid methyl ester:

15 Thionylchloride (19.4g, 163 mmol) was dropwise added to an ice cold solution of 4-amino salicylic acid (10.0g, 65.3 mmol) in methanol (200 mL). The reaction mixture was hereafter heated to 65°C for 6 days. The reaction mixture was concentrated in vacuo and the crude product was dissolved in a mixture of acetonitrile and water (1:1, 220 mL). Fmoc-Osu (22.0 g, 65.3 mmol) was added and the reaction mixture was stirred at 90°C for 16 hr. The reaction mixture was concentrated to 100 mL in vacuo, and water (50 mL) and ethyl acetate (250 mL) 20 added. The organic phase was isolated and washed with water (2x50 mL), a saturated solution of sodium chloride (2x50 mL), dried (magnesium sulphate) and concentrated in vacuo.

The residue was purified on silica (300 g) using ethyl acetate and n-heptane (1:2) as eluent. The product was recrystallized from methanol to give 4-(9H-fluoren-9-ylmethoxycarbonylamino)-2-hydroxybenzoic acid methyl ester. 25

m.p. 156-9°C

HPLC (Method 1)  $R_t$  = 31.7 min

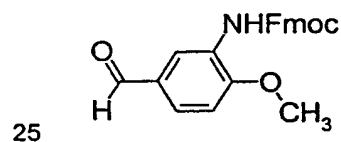
Micro analysis: calculated: C, 70.94; H, 4.92; N, 3.60%

30 found: C, 70.73; H, 4.98; N, 3.37%

4-(9H-Fluoren-9-ylmethoxycarbonylamino)-2-hydroxybenzoic acid methyl ester (4.36 g, 11.2 mmol) was dissolved in dimethylformamide (20 mL) and imidazole (1.92 g, 28 mmol) was added. tert-Butyldimethylsilylchloride (2.09 g, 13.4 mmol) dissolved in dimethylformamide (10 mL) was dropwise added and the reaction mixture was stirred at 20°C for 16 hr. The reaction mixture was poured into water (160 mL) and extracted with ethyl acetate (4x50 mL). The collected organic phases were washed with a saturated solution of sodium chloride (4x50 mL), dried (magnesium sulphate) and concentrated in vacuo. The residue was purified on silica (150 g) using ethyl acetate and n-heptane (15:85) as eluent. The isolated product (3.10 g, 6.15 mmol) was dissolved in dichloromethane (200 mL) under nitrogen. A solution of diisobutylaluminiumhydride (18.5 mL, 1.2M in toluene) was dropwise added 0-5°C. The mixture was stirred at 20°C for 3.5 hr, and quenched by dropwise addition of water at 0-5°C. After 2.5 hr at 20°C the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified on silica using ethyl acetate and n-heptane (1:3) as eluent. The isolated product (2.40 g) was dissolved in dichloromethane (120 mL) and manganese dioxide (4.39 g, 50.5 mmol) was added. The reaction mixture was stirred at 0°C for 16 hr and filtered. The filtrate was concentrated in vacuo and the residue purified on silica using ethyl acetate and n-heptane (15:85) as eluent to give 1.0 g of the title compound.

HPLC (Method 1)  $R_t$  = 30.7 min and 36.8 min

(5-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



Thionylchloride (10.3 g, 85 mmol) was dropwise added to an ice cold suspension of 3-amino-4-methoxybenzoic acid (9.48 g, 56.7 mmol) in methanol (180 mL). The reaction mixture was stirred at 20°C for 16 hr and concentrated in vacuo. Ethyl acetate (100 mL) and a saturated solution of sodium hydrogen carbonate (100 mL) were added and the organic phase was washed with saturated solutions of sodium hydrogen carbonate (2x40 mL), dried

(magnesium sulphate) and concentrated in vacuo. The crude product (7.7 g) and Fmoc-Osu (12.9 g, 38.2 mmol) were stirred in a mixture of acetonitrile and water (1:1, 75 mL) at 20°C for 16 hr, and at reflux for 3.5 hr. The reaction mixture was concentrated to half the volume and the precipitate isolated by filtering the mixture to give 15 g of intermediate crude product.

5

The product (5 g, 12 mmol) was dissolved in dichloromethane (400 mL) under nitrogen and a solution of diisobutylaluminium hydride (38 mL, 1.2M in toluene) was dropwise added at 0-5°C. The reaction mixture was stirred at 20°C for 16 hr and quenched by dropwise addition of water (23 mL) at 0-5°C. The reaction mixture was stirred at 20°C for 1.5 hr and filtered. The  
10 filtrate was concentrated in vacuo to give 4.9 g of intermediate product. The product (4.9 g) was suspended in dichloromethane (180 mL) and manganese dioxide (11.2 g, 129 mmol) was added. The mixture was stirred for 16 hr at 20°C and filtered. The filtrate was concentrated in vacuo to give 4.3 g crude product that was purified on silica (150 g) using ethyl acetate and n-heptane (3:7) as eluent to give 1.9 g of the title compound.

15

m.p. 139-142°C

HPLC (Method 1)  $R_t$  = 29.8 min

Micro analysis: calculated: C, 73.98; H, 5.13; N, 3.75%

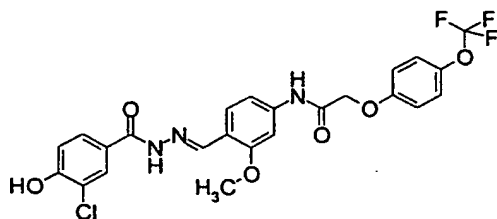
found: C, 73.45; H, 5.17; N, 3.72%

20

#### EXAMPLE 804:

25

N-(4-[3-Chloro-4-hydroxybenzoyl]hydrazonomethyl]-3-methoxyphenyl)-2-(4-trifluoromethoxyphenoxy)acetamide



Step 1: Coupling of aldehyde [building block 2] to resin[buildingblock 1]

0.75 g resin (Wang resin loaded with 3-chloro-4-hydroxybenzoic acid hydrazide) was swelled in dimethylformamide (6 mL) for 30 min and drained. The aldehyde (4-formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, 0.5 g, 1.36 mmol) dissolved in dimethylformamide (3 mL) was added followed by addition of triethylorthoformate (1.5 mL). The mixture was shaken for 16 hr at 20°C and drained. The resin was washed with dimethylformamide (5x4 mL), dichloromethane (5x4 mL) and dimethylformamide (5x4 mL). The coupling of the aldehyde was repeated twice.

Step 2: Deprotection of aniline

The resin was swelled in dimethylformamide (5 mL) and piperidine added (1.25 mL). After shaking for 30 min, the resin was drained and washed with dimethylformamide (5x4 mL), N-methylpyrrolidinone (5x4 mL) and dimethylformamide (5x4 mL).

Step 3: Coupling of acid [building block 3] to resin[building block 1][building block 2]

The resin[building block 1][building block 2] was swelled in dimethylformamide (2.5 mL) and the acid (4-trifluoromethoxy)phenoxy acetic acid (0.64 g, 2.7 mmol) was added together with diisopropylcarbodiimide (0.21 mL). After 5 min of shaking dimethylaminopyridine (0.34 mL) was added and the mixture was shaken for 3 hr and drained. The resin was washed with dimethylformamide (5x4 mL), dichloromethane (5x4 mL) and dimethylformamide (5x4 mL). The coupling of the acid was repeated twice, but with 16 hr reaction time for the repetition.

Step 4: Cleavage from the resin

The resin was swelled in dichloromethane (2.5 mL) and trifluoroacetic acid (2.5 mL) was added. After shaking for 1 hr the resin was drained. The eluent was collected and concentrated in vacuo. The residue was crystallized from methanol to give 0.2 g of the title compound.

m.p. 235-236.5°C

HPLC-MS (METHOD A)  $R_t$  = 13.5 min  $m/z$  = 538

Micro analysis: calculated: C, 53.59; H, 3.56; N, 7.81%

found: C, 53.57; H, 3.58; N, 7.51%

Further, a library of compounds of all the possible combinations of the above listed building blocks ([building block 1], [building block 2] and [building block 3]) was prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model  
5 384 HTS using the following ChemFile to control the operation of the synthesizer. The compounds are all expected to be present in the respective wells.

The four [building block 2] aldehydes, (4-Formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, (4-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, 3-  
10 (tert-Butyldimethylsilyloxy)-4-formylphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester and (5-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, were coupled to four individually batches of the resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) using the same procedure as described for step 1 in the example above. Subsequently the Fmoc deprotection of the anilino group was carried out as described in  
15 step 2 in the example above.

The four different examples of resin[building block 1][building block 2] thus prepared were equally distributed in the wells in the synthesizer prior to the initialization of the device. The attachment of the array of [building block 3] mentioned above was carried out in a fully  
20 combinatorial way with the four types of resin[building block 1][building block 2] using the general procedure as described in step 3 in the example above. The final cleavage was performed using the same general procedure as described in step 4 in the example above. During this cleavage step deprotection of acid sensible protection groups was also taken place. These two steps 3 and 4 were carried out (in several runs) on an ACT 496 HTS  
25 automated synthesizer using the following ChemFile to control the device.

ChemFile: C:\DATA\90250017.CHM

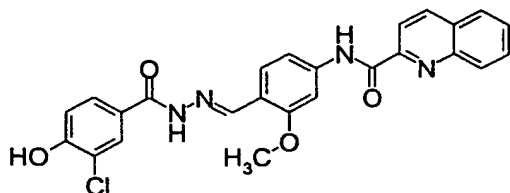
30 1 Empty RB1to96 for 2.000 minute(s)  
2 Flush Arm1 with NMParm1 and DCMarm1  
3  
4 REM Adding acids 1 to 36  
5

- 6 Dispense Sequence C:\act\ACID1-36.DSP with 1000ul to RB1to96 rack using NMParm1
- 7 Mix for 2.00 minutes at 600 rpm(s)
- 8 Pause
- 9 Mix for 2.00 minutes at 600 rpm(s)
- 5 10
- 11 REM Adding acids 37 to 48
- 12
- 13 Dispense Sequence ACI37-48.DSP with 1000ul to RB1to96 rack using NMParm1
- 14 Mix for 2.00 minutes at 600 rpm(s)
- 10 15
- 16 Pause
- 17
- 18 REM Adding DIC
- 19
- 15 20 Transfer 300ul from Monomer1to36[12]() to RB1to96[2-48] using NMParm1
- 21 Mix for 2.00 minutes at 600 rpm(s)
- 22 Transfer 300ul from Monomer1to36[13]() to RB1to96[50-96] using NMParm1
- 23 Mix for 10.00 minutes at 600 rpm(s)
- 24
- 20 25 REM Adding DMAP
- 26
- 27 Transfer 200ul from Monomer1to36[14]() to RB1to96[2-48] using NMParm1
- 28 Transfer 200ul from Monomer1to36[14]() to RB1to96[50-96] using NMParm1
- 29
- 25 30 REM Mixing overnight
- 31
- 32 Mix for 10.00 minutes at 600 rpm(s)
- 33 Wait for 20.000 minute(s)
- 34 Repeat from step 32, 150 times
- 30 35
- 36 REM wash
- 37
- 38 Empty RB1to96 for 2.000 minute(s)
- 39 Dispense System Fluid NMPdualarms\* 1000ul to RB1to96[1-96]
- 35 40 Mix for 3.00 minutes at 600 rpm(s)
- 41 Empty RB1to96 for 2.000 minute(s)
- 42 Repeat from step 39, 5 times
- 43
- 44 REM de fmoc
- 40 45 Mix for 3.00 minutes at 600 rpm(s)
- 46 Dispense Sequence C:\act\DEFMOC.DSP with 1500ul to RB1to96 rack using NMParm1
- 47 Mix for 15.00 minutes at 600 rpm(s)
- 48 Empty RB1to96 for 3.000 minute(s)
- 49 Empty RB1to24 for 3.000 minute(s)
- 45 50 Empty RB49to72 for 2.000 minute(s)
- 51 Pause
- 52
- 53 REM wash
- 54 Dispense System Fluid NMPdualarms\* 1000ul to RB1to96[1-96]

- 55 Mix for 3.00 minutes at 600 rpm(s)  
56 Empty RB1to96 for 3.000 minute(s)  
57 Repeat from step 54, 2 times  
58 Flush Arm1 with NMParm1 and DCMarm1, Arm2 with DCMarm2  
5 59 Dispense System Fluid DCMdualarm\* 1000ul to RB1to96[1-96]  
60 Mix for 3.00 minutes at 600 rpm(s)  
61 Empty RB1to96 for 3.000 minute(s)  
62 Repeat from step 59, 5 times  
63  
10 64 REM TFA CLEAVAGE  
65  
66 Mix for 1.00 minutes at 300 rpm(s)  
67 Transfer 1000ul from Reagent2[1]() to RBcleavage1to96[1-96] using DCMarm1  
68 Mix for 1.00 hours at 600 rpm(s)  
15 69 Empty RBcleavage1to96 for 30 second(s)  
70 Dispense System Fluid DCMdualarm\* 500ul to RBcleavage1to96[1-96]  
71 Mix for 5.00 minutes at 300 rpm(s)  
72 Empty RBcleavage1to96 for 30 second(s)  
73  
20  
Dispense sequence files C:\act\ACID1-36.DSP are subroutines that control the combinatorial addition of the amines into the 4 reaction blocks each containing 96 wells in the synthesizer.
- Examples of compounds from this library were characterized by HPLC-MS (molecular mass  
25 & retention time) and includes:

EXAMPLE 805:

- 30 Quinoline-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide

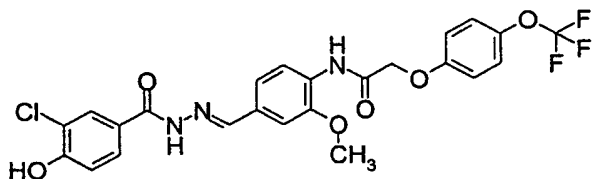


m.p. 236-238°C

HPLC (Method 1)  $R_t$ =26.2 min

- 35 EXAMPLE 806:

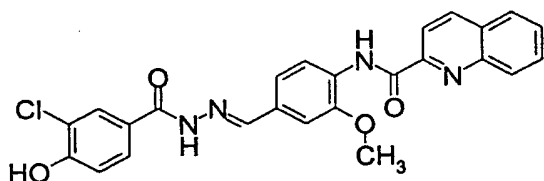
N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}-2-(4-trifluoromethoxyphenyl)acetamide



- 5 m.p. 216-218°C  
HPLC (Method 1)  $R_t$ =26.6 min

EXAMPLE 807:

- 10 Quinoline-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}amide

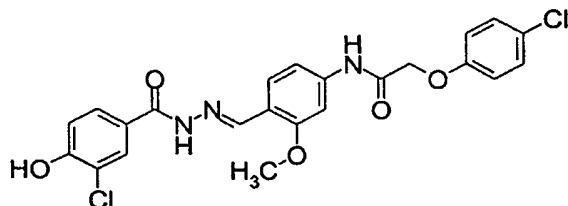


- m.p. 159-162°C  
HPLC (Method 1)  $R_t$ =27.7 min

15

EXAMPLE 808:

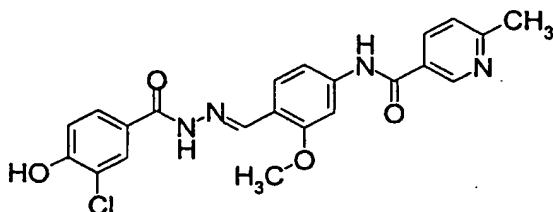
N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenoxy)acetamide



- 20 m.p. 216-218°C  
HPLC-MS (METHOD A)  $R_t$ =13.4 min,  $m/z$ =488

5 EXAMPLE 809:

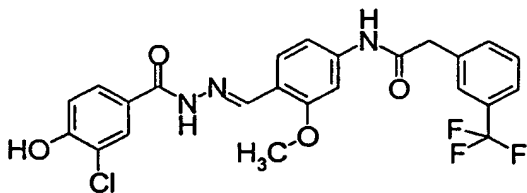
N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-6-methylnicotinamide



10 HPLC-MS (METHOD A)  $R_t$ =8.2 min,  $m/z$ =439

EXAMPLE 810:

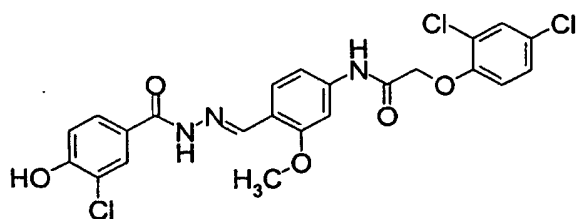
15 N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-trifluoromethylphenyl)acetamide



HPLC-MS (METHOD A)  $R_t$ =13.4 min,  $m/z$ =506

EXAMPLE 811:

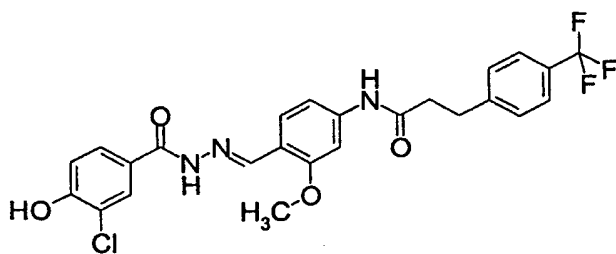
20 N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2,4-dichlorophenoxy)acetamide



HPLC-MS (METHOD A)  $R_t=14.3$  min,  $m/z=524$

5 EXAMPLE 812:

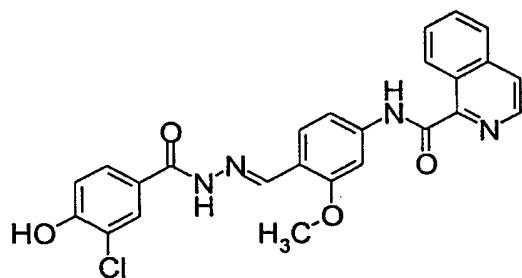
N-(4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)-3-(4-trifluoromethylphenyl)propionamide



10 HPLC-MS (METHOD A)  $R_t=14.0$  min,  $m/z=520$

EXAMPLE 813:

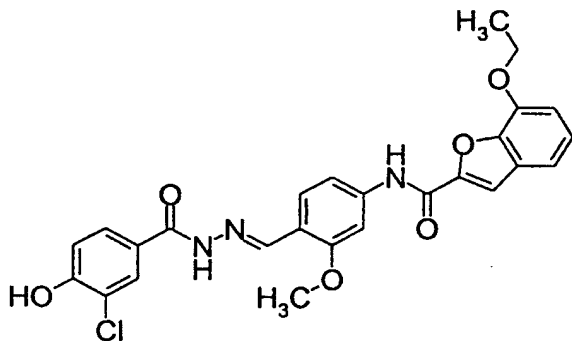
Isoquinoline-1-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



HPLC-MS (METHOD A)  $R_t=13.0$  min,  $m/z=475$

**EXAMPLE 814:**

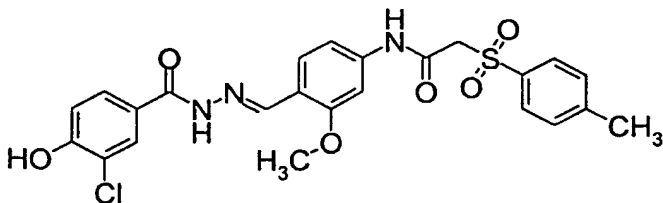
7-Ethoxybenzofuran-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



HPLC-MS (METHOD A)  $R_t$ =13.3 min,  $m/z$ =508

**EXAMPLE 815:**

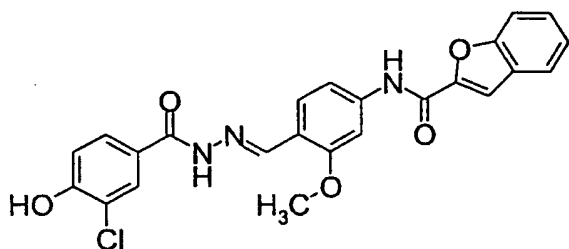
10 N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(toluene-4-sulonyl)acetamide



HPLC-MS (METHOD A)  $R_t$ =10.8 min,  $m/z$ =517

**EXAMPLE 816:**

Benzofuran-2-carboxylic acid {4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-amide

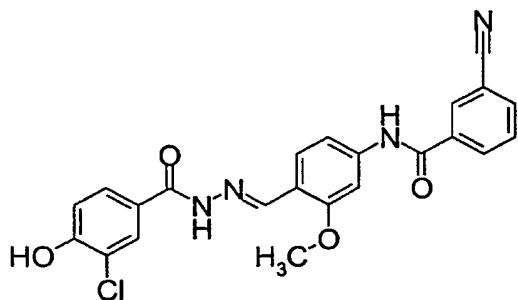


HPLC-MS (METHOD A)  $R_t=12.3$  min,  $m/z=465$

EXAMPLE 817:

5

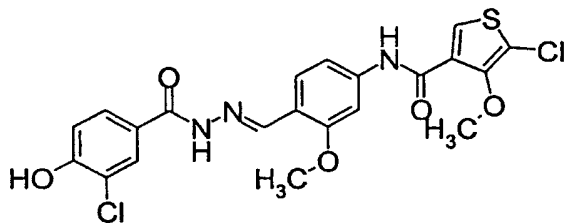
N-(4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)-3-cyanobenzamide



HPLC-MS (METHOD A)  $R_t=10.8$  min,  $m/z=450$

10 EXAMPLE 818:

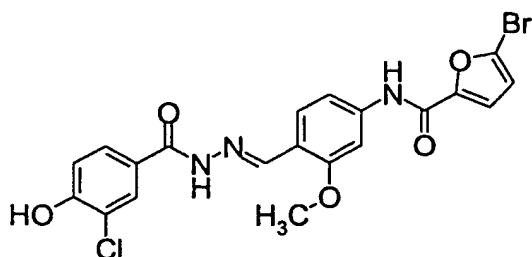
5-Chloro-4-methoxythiophene-3-carboxylic acid {4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



15 HPLC-MS (METHOD A)  $R_t=9.8$  min,  $m/z=495$

**EXAMPLE 819:**

5-Bromofuran-2-carboxylic acid {4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide

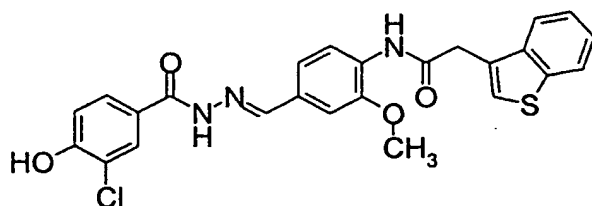


5 HPLC-MS (METHOD A)  $R_t=11.4$  min,  $m/z=494$

**EXAMPLE 820:**

2-Benzo[b]thien-3-yl-N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}acetamide

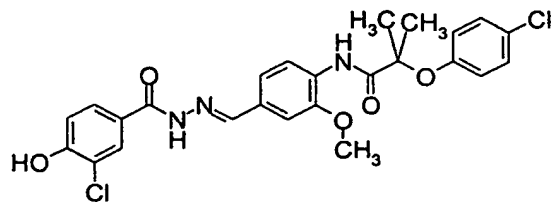
10



HPLC-MS (METHOD A)  $R_t=13.4$  min,  $m/z=494$

**EXAMPLE 821:**

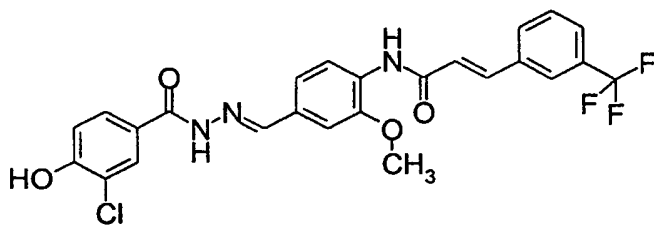
15 N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}-2-(4-chlorophenoxy)-2-methylpropionamide



HPLC-MS (METHOD A)  $R_t=14.7$  min,  $m/z=516$

**EXAMPLE 822:**

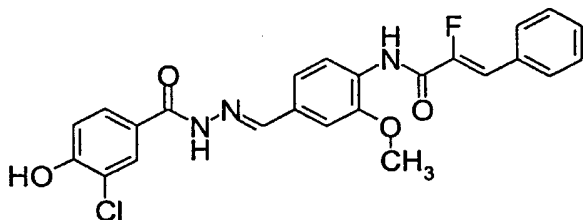
N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}-3-(3-trifluoromethylphenyl)acrylamide



HPLC-MS (METHOD A)  $R_t$ =14.3 min,  $m/z$ =518

**EXAMPLE 823:**

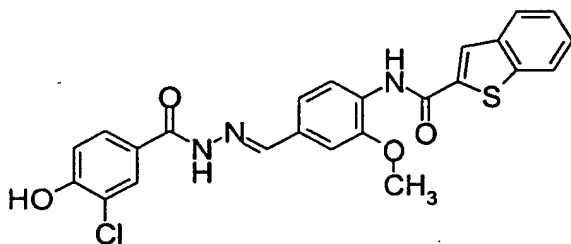
10 N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}-2-fluoro-3-phenylacrylamide



HPLC-MS (METHOD A)  $R_t$ =14.3 min,  $m/z$ =468

**EXAMPLE 824:**

2-Benzo[b]thiophene-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}amide



HPLC-MS (METHOD A)  $R_t=13.8$  min,  $m/z=480$

#### 5 HPLC Method 1.

The RP-HPLC analysis was performed using UV detection at 254 nm and a Merck Hibar LiChrosorb RP-18 (5  $\mu$ m) prepacked column (Cat. No. 50333), which was eluted at 1 mL/minute. Two solvent systems were used:

Solvent system I: 0.1% Trifluoroacetic acid in acetonitrile. Solvent system II: 0.1%

#### 10 Trifluoroacetic acid in water.

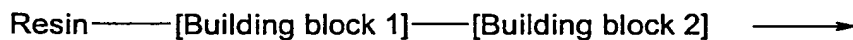
The column was equilibrated with a mixture composed of 20% of solvent system I and 80% of solvent system II. After injection of the sample a gradient of 20% to 80% of solvent system I in solvent system II was run over 30 minutes. The gradient was then extended to 100% of solvent system I over 5 minutes followed by isocratic elution with 100% of this system for 6

15 minutes.

#### General Procedure for Examples 825 to 875:

The compounds were prepared as single entities according to the following equation

20



and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the

25

following formula

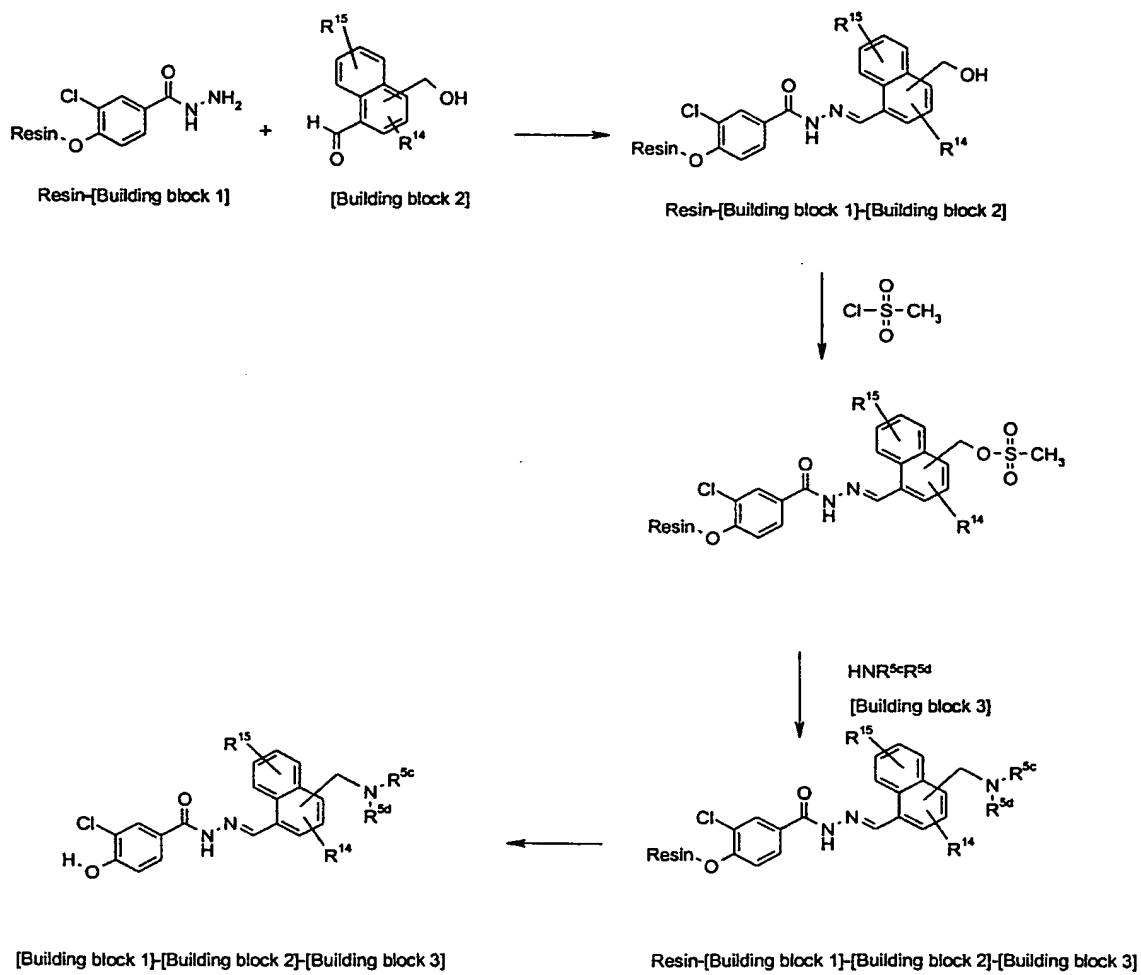
[Building block 1]—[Building block 2]—[Building block 3].

5 The following compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1]-[Building block 2] was done manually, whereas the attachment of [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

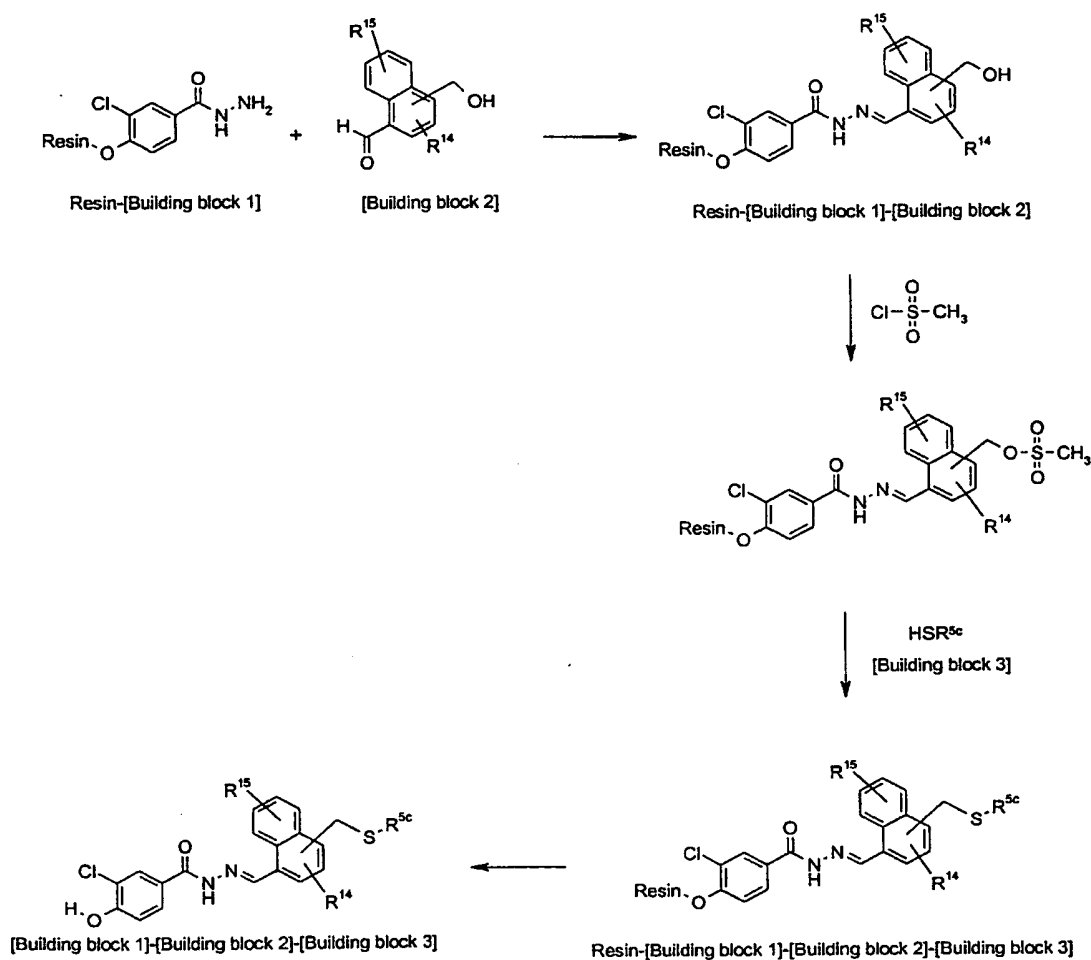
10 The starting resin, Resin-[Building block 1], was prepared as described above.

The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

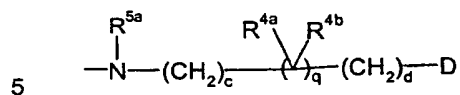
15 All compounds are based on successive attachment of [Building block 2] and [Building block 3] to Resin-[Building block 1] in a combinatorial way using a nucleophilic substitution reaction according to the following formulae, which are included in the general formula II:



and



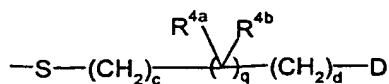
wherein  $R^{14}$ ,  $R^{15}$  are as defined for formula I and  $-\text{NR}^{5c}\text{R}^{5d}$  is



where  $R^{5a}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $c$ ,  $q$ ,  $d$ , and  $D$  are as defined for formula I or

$-\text{D}'$  where  $-\text{D}'$  is defined as a subset of  $-\text{D}$  that contains a primary or a secondary amine that can react as a nucleophile;

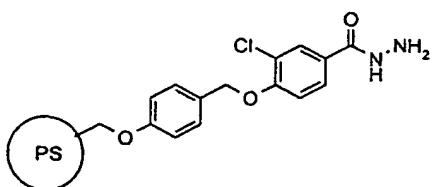
10 and  $-\text{SR}^{5c}$  is



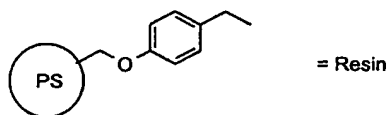
where  $\text{R}^{4a}$ ,  $\text{R}^{4b}$ ,  $c$ ,  $q$ ,  $d$ , and  $\text{D}$  are as defined for formula I or

-D' where -D' is defined as a subset of -D that contains a thiol that can react as a nucleophile.

The following resin, here depicted as Resin-[Building block 1] was used:

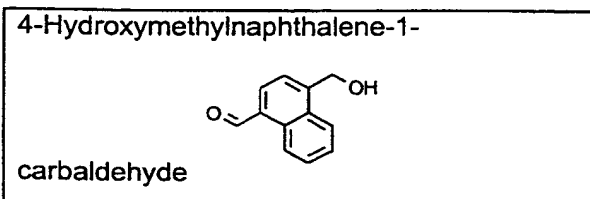


where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:



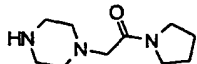
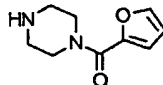
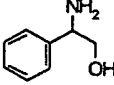
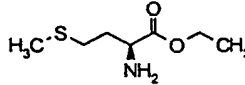
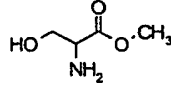
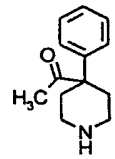
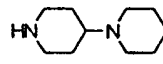
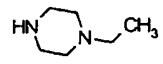
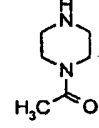

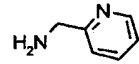
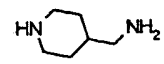
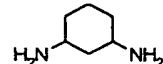

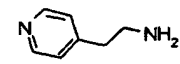
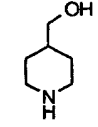

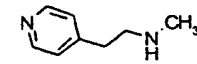
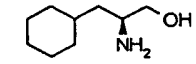
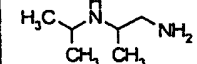
The following building blocks were used:

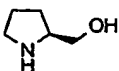
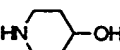
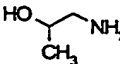
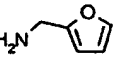
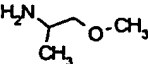
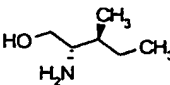
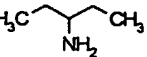
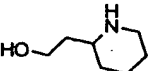
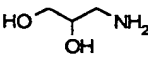


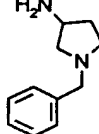
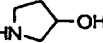
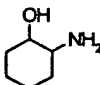


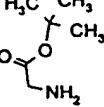
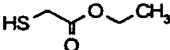




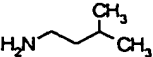

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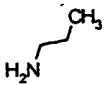

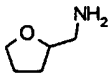
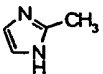
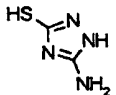
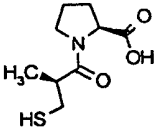
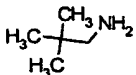
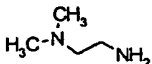
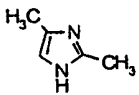

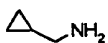



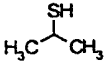
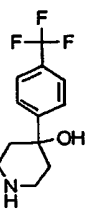
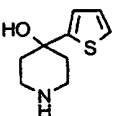
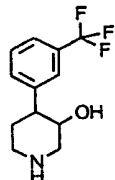


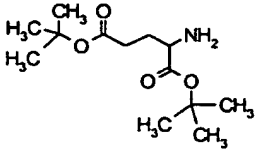
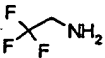
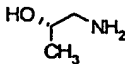
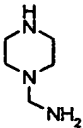
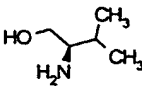

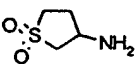
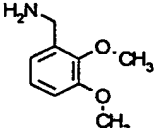
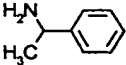
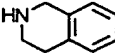
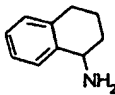
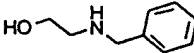

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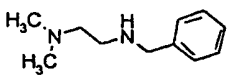
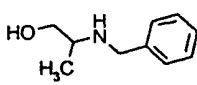
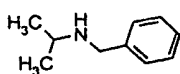
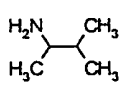
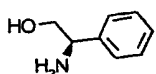
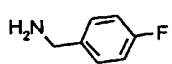
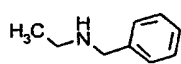
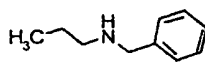
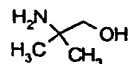
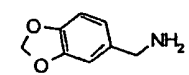
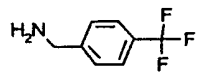
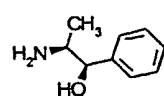
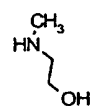
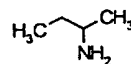
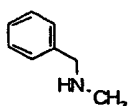
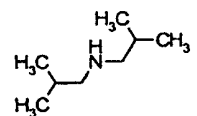

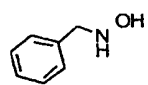
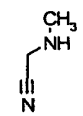
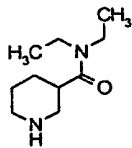
<p>(1,4'-Bipiperidine)-4'-carboxamide</p>	<p>2-Thiophenemethylamine</p>	<p>5-Methyl-2-furanmethylamine</p>
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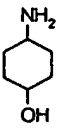
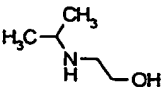
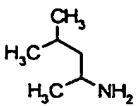
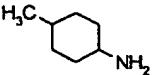
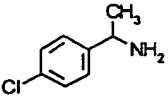
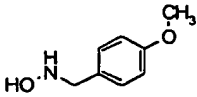
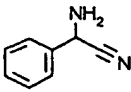
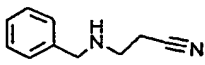
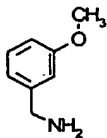
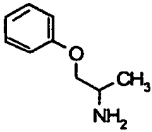
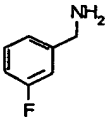
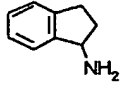
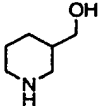
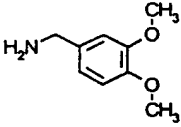
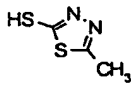
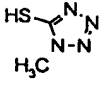
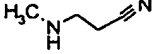
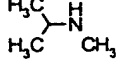

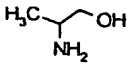
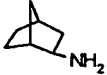
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L-Methionine ethyl ester 	DL-Serine methyl ester 	4-Acetyl-4-phenylpiperidine 
4-Piperidinopiperidine 	N-Ethylpiperazine 	1-Acetylpiperazine 
Piperazine 	2-(Aminomethyl)pyridine 	4-(Aminomethyl)piperidine 
1,3-Diaminocyclohexane 	Pyrrolidine 	
4-(2-Aminoethyl)pyridine 	4-(Hydroxymethyl)piperidine 	Thiomorpholine 
2-(2-Methylaminoethyl)-pyridine 	(s)-2-Amino-3-cyclohexyl-1-propanol 	3-Isopropylamino-n-propylamine 

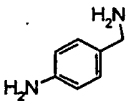



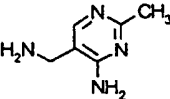
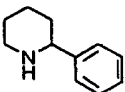
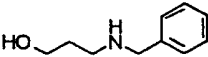
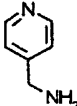
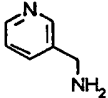
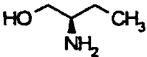
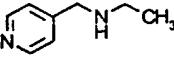
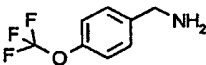
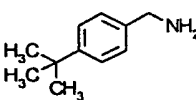
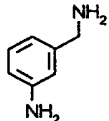
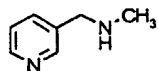
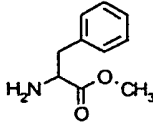
<b>L-Prolinol</b> 	<b>4-Hydroxypiperidine</b> 	<b>1-Amino-2-propanol</b> 
<b>Furfurylamine</b> 	<b>2-Methoxyisopropylamine</b> 	<b>L-Isoleucinol</b> 
<b>3-Aminopentane</b> 	<b>2-Piperidineethanol</b> 	<b>3-Amino-1,2-propanediol</b> 
<b>Cyclopropylamine</b> 	<b>Ethylenediamine</b> 	<b>1-Benzyl-3-Aminopyrrolidine</b> 
<b>3-Pyrrolidinol</b> 	<b>2-Aminocyclohexanol</b> 	<b>Morpholine</b> 
<b>3-Mercaptopropionic acid</b> 	<b>Glycine <u>tert</u> butylester</b> 	<b>3-Mercaptopropionic acid ethyl ester</b> 
<b>Ethylamine</b> 	<b>Methylamine</b> 	<b>2-Aminoethanol</b> 
<b>Isopropylamine</b> 	<b>Isopentylamine</b> 	<b>Dimethylamine</b> 

Propylamine 	Cyclopentylamine 	2-Furanylmethylamine 
2-Methylimidazole 	3-Amino-5-mercapto-1,2,4-triazole 	Captopril 
2,2-Dimethylpropylamine 	N,N-Dimethylethylene-diamine 	2,4-Dimethylimidazole 
3-Mercapto-1H-1,2,4-triazol 	Cyclopropylmethylamine 	Cyclobutylamine 
4-Mercaptopyridine 	Thiazolidine 	Isopropylmercaptane 
4-(4-Trifluoromethylphenyl)- 4-piperidinol 	4-(2-Thienyl)-4-piperidinol 	4-(3-Trifluoromethylphenyl)- 3-piperidinol 

Glutamic Acid di <u>tert</u> butylester 	2,2,2-Trifluoroethylamine 	S-1-amino-2-propanol 
4-(Aminomethyl)-piperidine 	D-Valinol 	Thiophene-2-ethylamine 
Tetrahydro-3-thiophenamine 1,1-dioxide 		
2,3-Dimethoxybenzylamine 	Alfa-methylbenzylamine 	1,2,3,4-Tetrahydroisoquinoline 
1,2,3,4-Tetrahydro-1-naphthylamine 	N-Benzylethanolamine 	4-Methoxybenzylamine 

<b>N'-Benzyl-N,N-dimethylethylenediamine</b> 	<b>2-Benzylamino-1-propanol</b> 	
<b>N-Isopropylbenzylamine</b> 	<b>1,2-Dimethylpropylamine</b> 	<b>D-(-)-alpha-Phenylglycinol</b> 
<b>4-Fluorobenzylamine</b> 	<b>N-Ethylbenzylamine</b> 	<b>N-(n-propyl) Benzylamine</b> 
<b>2-Amino-2-methyl-1-propanol</b> 	<b>Piperonylamine</b> 	<b>4-(Trifluoromethyl)benzylamine</b> 
<b>(-)-Norephedrine</b> 	<b>2-Methylaminoethanol</b> 	<b>2-Butylamine</b> 
<b>Benzylmethylamine</b> 	<b>Diisobutylamine</b> 	<b>Cyclohexylamine</b> 
<b>N-Benzylhydroxylamine</b> 	<b>Methylaminoacetonitril</b> 	<b>N,N-Diethyl nipecotamide</b> 

<b>4-Aminocyclohexanol</b> 	<b>2-Isopropylaminoethanol</b> 	<b>1,3-Dimethylbutanamine</b> 
<b>4-Methylcyclohexylamine</b> 	<b>Alfa-methyl-4-chlorobenzylamine</b> 	<b>4-Methoxybenzylhydroxylamine</b> 
<b>2-Phenylglycinonitrile</b> 	<b>3-(Benzylamino)propionitrile</b> 	<b>3-Methoxybenzylamine</b> 
<b>1-Methyl-2-phenoxyethylamine</b> 	<b>3-Fluorobenzylamine</b> 	<b>1-Aminoindan</b> 
<b>3-Piperidinemethanol</b> 	<b>3,4-Dimethoxybenzylamine</b> 	<b>2-Mercapto-5-methylthiadiazole</b> 
<b>1-Methyl-5-mercaptotetrazole</b> 	<b>3-Methylaminopropionitril</b> 	<b>Isopropylmethylamine</b> 
<b>2-Mercaptothiazole</b> 	<b>2-Amino-1-propanol</b> 	<b>exo-2-Aminonorbornane</b> 

<p>4-Aminobenzylamine</p> 	<p>2-Mercaptoimidazol</p> 	<p>2-Mercapto-1-methylimidazol</p> 
<p>3-Mercapto-4-methyl-1,2,4-triazol</p> 	<p>2-Methyl-4-amino-5-aminomethylpyrimidine</p> 	<p>2-Phenylpiperidine</p> 
<p>3-benzylamino-1-propanol</p> 	<p>4-Aminomethylpyridine</p> 	<p>3-Aminomethylpyridine</p> 
<p>R-2-Amino-1-propanol</p> 	<p>4-(Ethylaminomethyl)pyridine</p> 	<p>4-Trifluoromethoxybenzyl-amine</p> 
<p>4-<u>tert</u>-Butylbenzylamine</p> 	<p>3-Aminobenzylamine</p> 	<p>3-(Methylaminomethyl)-pyridine</p> 
<p>DL-Phenylalanine methyl ester</p> 		

Preparation of resin-[Building block 1]:

This resin was prepared as described above.

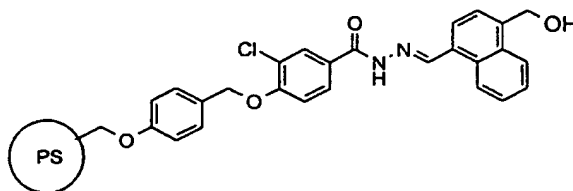
5 Preparation of 4-hydroxymethylnaphtaldehyde ([Building block 2]):

The preparation of this compound is described above.

Preparation of resin-[Building block 1]-[Building block 2]:

10

Preparation of resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide:



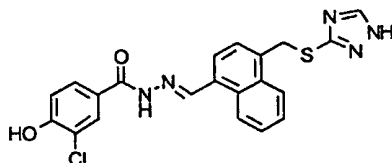
15

Resin-[Building block 1] (4 g) was suspended in DMF (40 mL) and was allowed to swell for 15 min. and then washed with DMF (2 x 40 mL), DCM (3 x 40 mL) and DMSO (2 x 40 mL). The solvent was removed by filtration. 1.488 g (8 mmol) 4-hydroxymethylnaphtaldehyde was dissolved in 40 mL DMSO and was added to the resin followed by 4 mL glacial acetic acid.

20 The suspension was shaken for 16 hours at 25 °C. The resin was successively washed with DMSO (2 x 40 mL), THF (3 x 40 mL), CH<sub>3</sub>OH (40 mL), CH<sub>2</sub>Cl<sub>2</sub> (40 mL), CH<sub>3</sub>OH (40 mL), CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and dried *in vacuo* at 40 °C for 16 hours to afford resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide.

25 EXAMPLE 825:

3-chloro-4-hydroxybenzoic acid (4-(1H-1,2,4-Triazol-3-ylsulfanylmethyl)naphthylmethylene)hydrazide



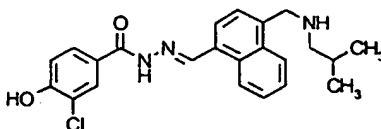
The resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)-hydrazide (resin-[Building block 1]-[Building block 2]) (2 g, ~ 2 mmoles) was swelled in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) for 15 min, then washed twice with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). 8 mL CH<sub>2</sub>Cl<sub>2</sub> and 8 ml diisopropylethylamine was subsequently added and the suspension was cooled to 0 °C. Methanesulfonylchloride (2 mL) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) and added to the suspension. The mixture was allowed to react at 0 °C for 30 min, then at 25 °C for 1 hour. The resin was isolated by filtration and washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL) and N-methyl-2-pyrrolidone (2 x 20 mL). 1H-1,2,4-Triazole-3-thiol (0.8 g) and KI (0.4 g) was dissolved in a mixture of 10 mL N-methyl-2-pyrrolidone and 10 mL dimethylsulfoxide and was added to the resin. Then 4 mL diisopropylethylamine was added and the mixture was shaken at 25 °C for 2 days. The solvent was removed by suction and the resin was washed with N-methyl-2-pyrrolidone (3 x 20 mL) THF (3 x 20 mL), CH<sub>3</sub>OH (20 mL), CH<sub>2</sub>Cl<sub>2</sub> (20 mL), CH<sub>3</sub>OH (20 mL), CH<sub>2</sub>Cl<sub>2</sub> (4 x 20 mL). The compound was cleaved from the resin by shaking for 1 hour at 25 °C with a 50% solution of trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The mixture was filtered and the resin was extracted with acetonitrile (20 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of CH<sub>3</sub>OH (10 mL) and acetonitrile (10 mL) and concentrated in vacuo. The residue was treated with CH<sub>3</sub>OH (4 mL) at 25 °C providing an off-white precipitate which was isolated by filtration. The solid was washed with CH<sub>3</sub>OH (3 x 2 mL) and dried in vacuo at 40 °C. This afforded 275 mg of the title compound.

HPLC-MS (METHOD B): R<sub>t</sub> = 2.48 min; m/z = 438 (M+1).

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ = 4.9 (2H, s), 7.1 (1H, d), 7.5-7.9 (5H, m), 8.0 (1H, s), 8.25 (1H, d), 8.9 (1H, d), 9.1 (1H, s), 11.0 (1H, s), 11.8 (1H, s)

#### EXAMPLE 826:

3-Chloro-4-hydroxybenzoic acid (4-(isobutylaminomethyl)naphthylmethylene)hydrazide

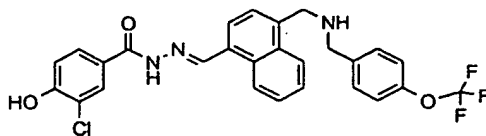


The resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthyl-methylene)hydrazide (resin-[Building block 1]-[Building block 2]) (50 mg, ~ 0.05 mmoles) was swelled in  $\text{CH}_2\text{Cl}_2$  (1 mL) for 15 min, then washed with  $\text{CH}_2\text{Cl}_2$  (2 x 0.5 mL). 0.4 mL  $\text{CH}_2\text{Cl}_2$  and 0.4 mL diisopropylethylamine was subsequently added and the suspension was cooled to 0 °C. Methanesulfonylchloride (0.1 mL) was dissolved in  $\text{CH}_2\text{Cl}_2$  (0.3 mL) and added to the suspension. The mixture was allowed to react at 0 °C for 30 min, then at 25 °C for 1 hour. The resin was isolated by filtration and washed with  $\text{CH}_2\text{Cl}_2$  (2 x 0.5 mL) and DMSO (0.5 mL). DMSO (0.5 mL) was added followed by 50  $\mu\text{L}$  isobutylamine and 100  $\mu\text{L}$  diisopropylethylamine. The mixture was shaken at 25 °C for 16 hours, filtered and washed successively with DMSO (2 x 0.5 mL), THF (3 x 0.5 mL),  $\text{CH}_3\text{OH}$  (0.5 mL),  $\text{CH}_2\text{Cl}_2$  (0.5 mL),  $\text{CH}_3\text{OH}$  (0.5 mL),  $\text{CH}_2\text{Cl}_2$  (4 x 0.5 mL). The compound was cleaved from the resin by shaking for 1 hour at 25 °C with a 50% solution of trifluoroacetic acid in  $\text{CH}_2\text{Cl}_2$  (1 mL). The mixture was filtered and the resin was extracted with acetonitrile (1 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of  $\text{CH}_3\text{OH}$  (0.5 mL) and acetonitrile (0.5mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD B):  $R_t$  = 4.20 min;  $m/z$  = 410 (M+1)

## 20 EXAMPLE 826:

3-Chloro-4-hydroxybenzoic acid ((4-(4-trifluoromethoxybenzylamino)methyl)naphthyl-methylene)hydrazide



25 Resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide: (resin-[building block 1]-[building block 2]) (50 mg) was swelled in a 1:1 mixture of  $\text{CH}_2\text{Cl}_2$  and N-methyl-2-pyrrolidone (0.5 mL) for 15 minutes and then washed with  $\text{CH}_2\text{Cl}_2$  (3 x 0.5 mL). 800  $\mu\text{L}$  of a 1:1 mixture of  $\text{CH}_2\text{Cl}_2$  and diisopropylethylamine was added to the resin

which subsequently was cooled to -3 °C. A solution of 100 µL methanesulfonylchloride dissolved in 300 µL was added and allowed to react at -3 °C for 30 minutes then at 25 °C for 1 hour. Filtration of the resin was followed by washing with CH<sub>2</sub>Cl<sub>2</sub> (2 x 1 mL) and N-methyl-2-pyrrolidone (2 x 0.5 mL). 600 µL of a solution of 4-trifluoromethoxybenzylamine (45.8 mg, 0.24 mmol, 0.4M) and KI (10 mg, 0.06 mmol, 0.1M) in N-methyl-2-pyrrolidone (0.5 mL) and diisopropylethylamine (0.1 mL) was added and allowed to react at 25 °C for 16 hours. The resin was isolated by filtration and washed successively with N-methyl-2-pyrrolidone (5 x 0.5 mL), THF (3 x 0.8 mL), CH<sub>3</sub>OH (0.8 mL), CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL), CH<sub>3</sub>OH (0.8 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 x 0.8 mL). The compound was cleaved from the resin by shaking 1 hour at 25 °C with a solution of 50% trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was filtered and the resin was extracted with acetonitrile (1 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of CH<sub>3</sub>OH (0.5 mL) and acetonitrile (0.5mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD A): R<sub>t</sub> = 10.07 min; m/z = 528 (M+1)

#### EXAMPLES 828 TO 875:

A library of compounds of all the possible combinations of the above listed building blocks ([building block 1], [building block 2] and [building block 3]) was prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model 384 HTS using the following ChemFile to control the operation of the synthesizer. The compounds are all expected to be present in the respective wells.

A suspension of the resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide: (resin-[building block 1]-[building block 2]) (50 mg) in a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and N-methyl-2-pyrrolidone (0.5 mL) is equally distributed in the wells in the synthesizer prior to the initialization of the device.

30

ChemFile C:\ACT\_1328\MAIN.CHM

1 REM Nucleophilic displacement of benzylic alcohol

2 REM via mesylation  
3  
4  
5 REM Dipense resin bound benzylic alchohol to wells  
5 6  
7  
8 REM Setup Diluter1=DCM, D2=NMP (N-methyl-2-pyrrolidone), D3=NMP, D4=DCM  
9 REM Adjust pressure  
10 REM Add 100 mL DIEA/DCM 1:1 mixture to Reagent1  
10 11 REM Add 70 mL MsCl/DCM 1:3 mixture to Reagent2  
12 REM Add 100 mL TFA/DCM 1:1 mixture to Reagent3  
13 REM Add 100 mL CH3CN to Reagent4  
14 REM Nitrogen for cooling  
15  
15 16 Pause  
17 REM Initialising...  
18  
19 REM Subroutine Empty1\_72\_3min is called twice to remove DCM/NMP from dispensed resin  
20 20 Go to ChemFile MTY72\_3M.CHM, line 1  
21 Go to ChemFile MTY72\_3M.CHM, line 1  
22  
23 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and with Flush Diluter 4  
25 24  
25 REM Washing with DCM, 3 times  
26 Dispense System Fluid Disdu1\_4\* 500ul to RB1\_1to96[1-72]  
27 Mix "RB1\_1to96" for 3.00 minutes at 300 rpm(s) and wait.  
28 REM Subroutine Empty1\_72\_3min  
30 29 Go to ChemFile MTY72\_3M.CHM, line 1  
30 Repeat from step 26, 2 times  
31  
32 REM Adding DCM/DIEA mixture from Reagent1  
33 Transfer 800ul from REAGENT\_1[1](DCM/DIEA) to RB1\_1to96[1-72] using Flush Diluter1  
35 34 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
35 Set Temperature of rack "RB1\_1to96" to -3.0 degrees Celsius and wait for Temperera-  
ture to reach setpoint  
36 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
37 REM Ensure complete cooling  
40 38 Wait for 15.000 minute(s)  
39  
40 REM Adding mesylchloride  
41 Transfer 400ul from REAGENT\_2[1](MsCl/DCM) to RB1\_1to96[1-72] using Flush Diluter1  
42 REM Reacts 30 min @ -3 °C  
45 43 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
44 Wait for 4.000 minute(s)  
45 Repeat from step 43, 5 times  
46  
47 REM Reacts 60 min @ 25 C

48 Set Temperature of rack "RB1\_1to96" to 25.0 degrees Celsius and wait for Temperature to reach setpoint  
49 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
50 Wait for 4.000 minute(s)  
5 51 Repeat from step 46, 11 times  
52  
53 REM Subroutine Empty1\_72\_3min  
54 Go to ChemFile MTY72\_3M.CHM, line 1  
55  
10 56 REM Initiate washing procedure, 2XDCM  
57 Dispense System Fluid Disdu1\_4\* 1000ul to RB1\_1to96[1-72]  
58 Mix "RB1\_1to96" for 3.00 minutes at 300 rpm(s) and wait.  
59 Go to ChemFile MTY72\_3M.CHM, line 1  
60 Repeat from step 57, 1 times  
15 61  
62 REM NMP wash  
63  
64 Dispense System Fluid Disdu2\_3\* 500ul to RB1\_1to96[1-72]  
65 Mix "RB1\_1to96" for 5.00 minutes at 300 rpm(s) and wait.  
20 66 Go to ChemFile MTY72\_3M.CHM, line 1  
67  
68 Go to ChemFile MTY72\_3M.CHM, line 1  
69 Repeat from step 64, 1 times  
70  
25 71 REM Make sure that nucleophiles are dissolved and ready for addition  
72 Pause  
73  
74 Dispense Sequence C:\ACT\_1328\R2-A.DSP with 600ul to RB1\_1to96 rack using Flush Diluter 2  
30 75 REM Nucleophiles react @ 25 C for 16 hr  
76 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
77 Wait for 4.000 minute(s)  
78 Repeat from step 76, 11 times  
79 Repeat from step 76, 15 times  
35 80  
81 REM End of reaction  
82 Go to ChemFile MTY72\_3M.CHM, line 1  
83 Go to ChemFile MTY72\_3M.CHM, line 1  
84  
40 85 REM Commence final washing procedure  
86 Dispense System Fluid Disdu2\_3\* 500ul to RB1\_1to96[1-72]  
87 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
88 Go to ChemFile MTY72\_3M.CHM, line 1  
89 Go to ChemFile MTY72\_3M.CHM, line 1  
45 90 Repeat from step 86, 4 times  
91  
92 REM Change systemfluids:  
93 REM \* Diluter2: THF  
94 REM \* Diluter3: MeOH

95 Pause  
96  
97 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and Flush Diluter 4  
5 98 REM THF wash 3 times  
99 Dispense System Fluid Flush Diluter 2 800ul to RB1\_1to96[1-72]  
100 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
101 Go to ChemFile MTY72\_3M.CHM, line 1  
102 Go to ChemFile MTY72\_3M.CHM, line 1  
10 103 Repeat from step 99, 2 times  
104  
105 REM Alternating MeOH/DCM wash, 2 cycles  
106 Dispense System Fluid Flush Diluter 3 800ul to RB1\_1to96[1-72]  
107 Mix "RB1\_1to96" for 3.00 minutes at 300 rpm(s) and wait.  
15 108 Go to ChemFile MTY72\_3M.CHM, line 1  
109  
110 Dispense System Fluid Disdu1\_4\* 800ul to RB1\_1to96[1-72]  
111 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
112 Go to ChemFile MTY72\_3M.CHM, line 1  
20 113 Go to ChemFile MTY72\_3M.CHM, line 1  
114  
115 Repeat from step 106, 1 times  
116  
117 Dispense System Fluid Disdu1\_4\* 800ul to RB1\_1to96[1-72]  
25 118 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
119 Go to ChemFile MTY72\_3M.CHM, line 1  
120 Repeat from step 117, 1 times  
121  
122 REM Washing procedure has ended  
30 123  
124 REM Setup for cleavage:  
125 REM \* Cleavage vials  
126 REM \* Lower pressure  
127 REM \* Add 100 mL TFA/DCM 1:1 mixture to Reagent3  
35 128 REM \* Add 100 mL CH3CN to Reagent4  
129 Pause  
130  
131 REM Adding cleavage solution, 1hr  
132 Transfer 1000ul from REAGENT\_3[1](TFA/DCM) to RB1\_1to96[1-72] using Flush Di-  
40 luter1  
133 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
134 Wait for 4.000 minute(s)  
135 Repeat from step 133, 11 times  
136 REM PULSE EMPTY!  
45 137 Go to ChemFile PULSEMP1.CHM, line 1  
138  
139 REM Washing with CH3CN  
140 Transfer 500ul from REAGENT\_4[1](CH3CN) to RB1\_1to96[1-72] using Flush Diluter1  
141 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.

142 REM PULSE EMPTY!  
143 Go to ChemFile PULSEMP1.CHM, line 1  
144  
145 REM The End  
5 146

The following chemfile is called to empty the wells of the reaction block.:

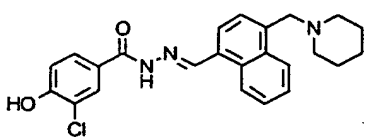
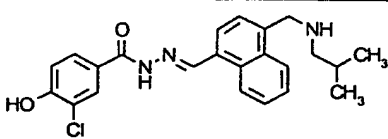
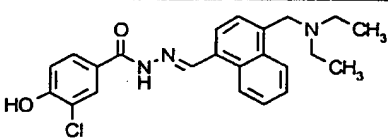
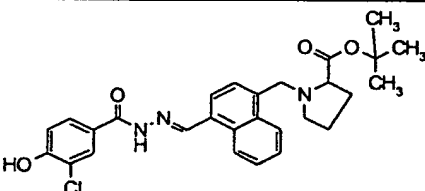
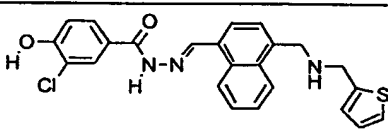
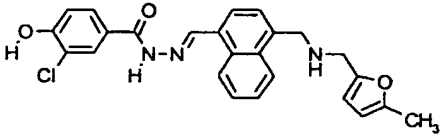
ChemFile C:\ACT\_1328\MTY72\_3M.CHM  
10  
1 REM Subroutine Empty1\_72\_3min  
2 Empty RB1\_1to96 for 5.000 minute(s)  
3 Return

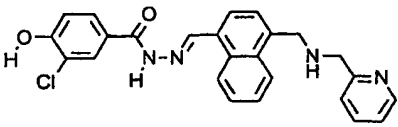
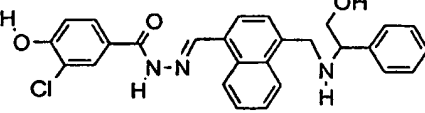
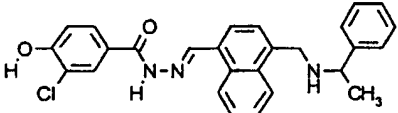
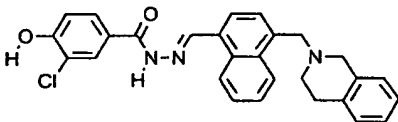
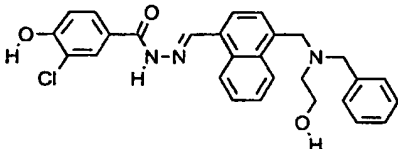
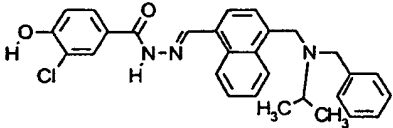
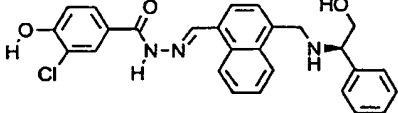
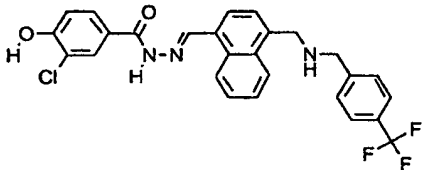
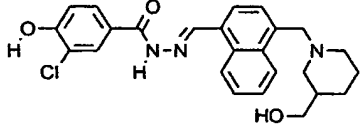
15 The following chemfile is called to empty the wells of the reaction block into the cleavage vials containing the final product in a controlled manner.

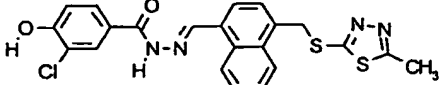
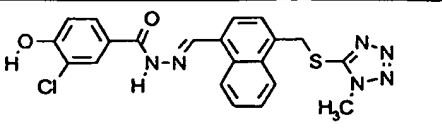
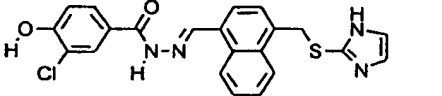
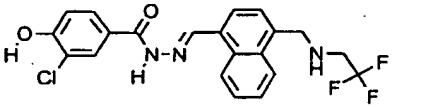
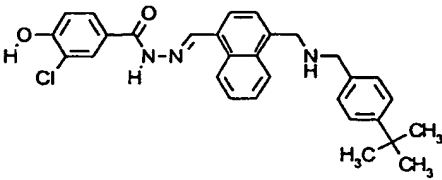
ChemFile C:\ACT\_1328\PULSEMP1.CHM  
20 1 Empty RB1\_1to96 for 1 second(s)  
2 Wait for 4 second(s)  
3 Repeat from step 1, 11 times  
4 Empty RB1\_1to96 for 5.000 minute(s)  
5 Return  
25

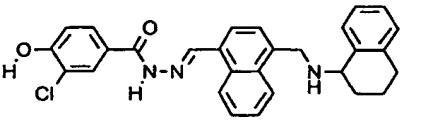
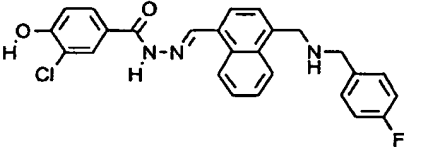
Dispense sequence C:\ACT\_1328\R2-A.DSP is a subroutine that controls the combinatorial addition of the amines into the reaction block in the synthesiser.

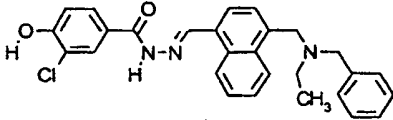
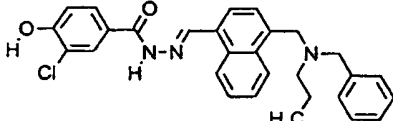
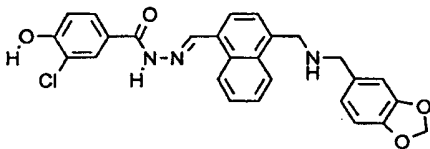
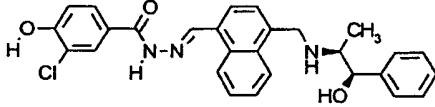
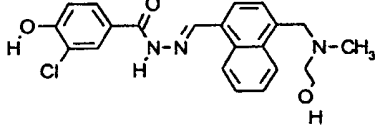
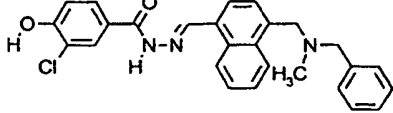
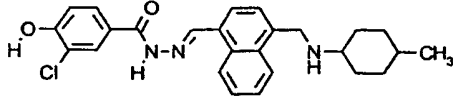
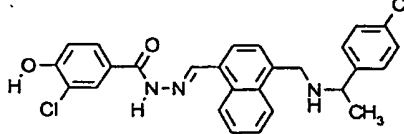
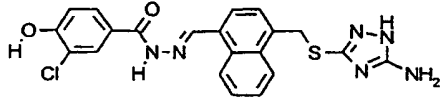
30 Examples of compounds from this library were characterised by HPLC-MS (molecular mass & retention time) including the following examples 828 to 875:

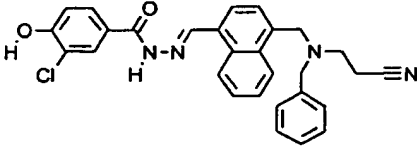
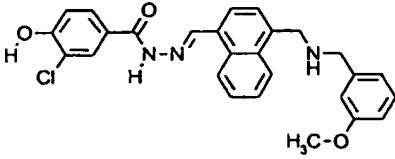
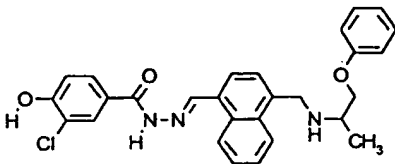
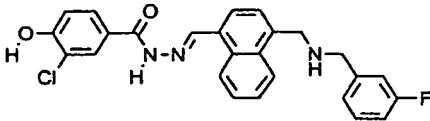
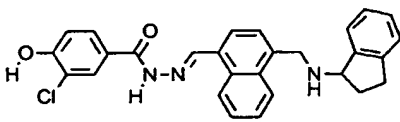
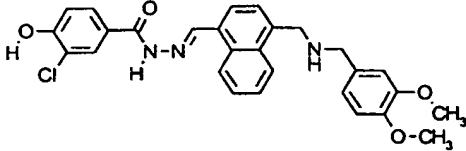
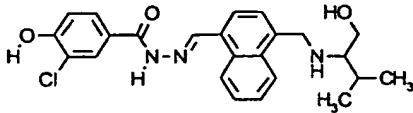
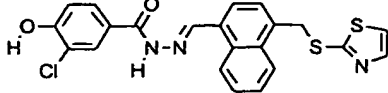
Ex No.	Structure	HPLC-MS (METHOD B) m/z (M+1)	HPLC-MS (METHOD B) R <sub>t</sub> (minutes)
828		422	6.10
829		410	4.20
830		410	4.93
831		508	13.30
832		450	7.87
833		448	7.07

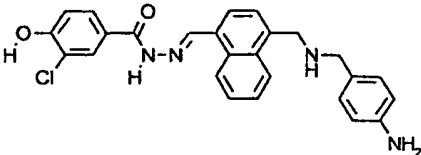
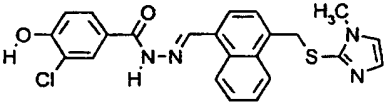
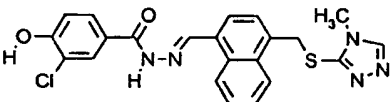
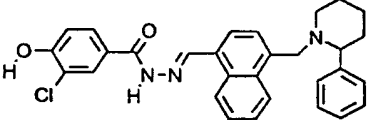
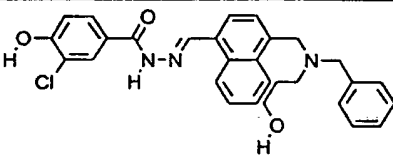
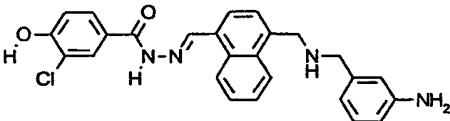
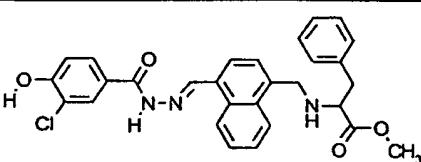
834		474	6.10
835		445	3.32
836		458	9.55
837		470	14.13
838		488	9.85
839		486	17.00
840		474	6.35
841		512	12.82
842		452	3.25

843		468	6.25
844		453	4.87
845		437	2.68
846		436	7.88
847		500	14.12

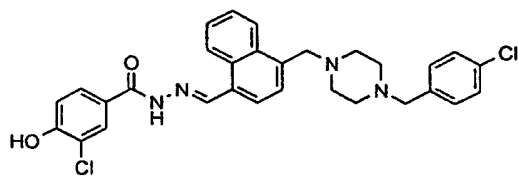
Ex No.	Structure	HPLC-MS (METHOD A) m/z (M+1)	HPLC-MS (METHOD A) R <sub>t</sub> (minutes)
848		484	9.80
849		462	9.38

850		472	9.37
851		486	9.55
852		488	9.18
853		488	9.37
854		412	7.83
855		458	9.30
856		450	9.62
857		492	10.03
858		453	8.90

859		497	10.73
860		474	9.15
861		488	9.55
862		462	9.27
863		470	9.43
864		504	8.98
865		440	8.35
866		454	12.90

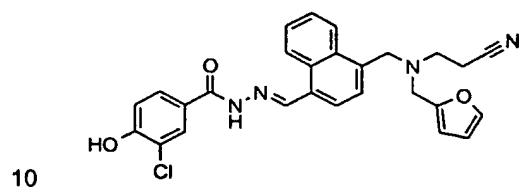
867		459	7.63
868		451	8.45
869		452	9.31
870		498	9.65
871		502	9.03
872		459	7.60
873		516	9.33

## EXAMPLE 874:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 2.37 (m, 8H), 3.44 (s, 2H), 3.90 (s, 2H), 7.10 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 7.4 Hz, 1H), 7.67 (m, 2H), 7.81 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 8.36 (dd, J = 1.7, 7.0 Hz, 1H), 8.83 (d, J = 8.0 Hz, 1H), 9.08 (s, 1H), 10.99 (s, 1H), 11.78 (s, 1H). MS (APCI, pos.):  
5 547.1, 550.1

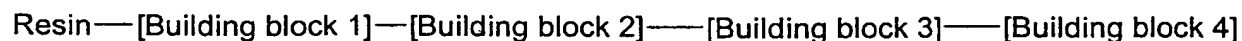
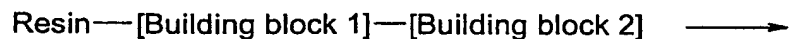
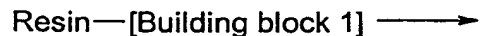
## EXAMPLE 875:



<sup>1</sup>H NMR (DMSO-D<sub>6</sub>) δ 2.66 - 2.75 (m, 4H), 3.69 (s, 2H), 4.06 (s, 2H), 6.36 (m, 1H), 6.40 (m, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.51 - 7.66 (m, 4H), 7.77 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.98 (s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.80 (d, J = 8.5 Hz, 1H), 9.04 (s, 1H), 10.94 (s, 1H), 11.77 (s, 1H). MS (APCI, pos.): 485.1, 487.1  
15

General Procedure for Examples 876 to 877:

The compounds were prepared as single entities according to the following equation  
20



and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the  
25 following formula

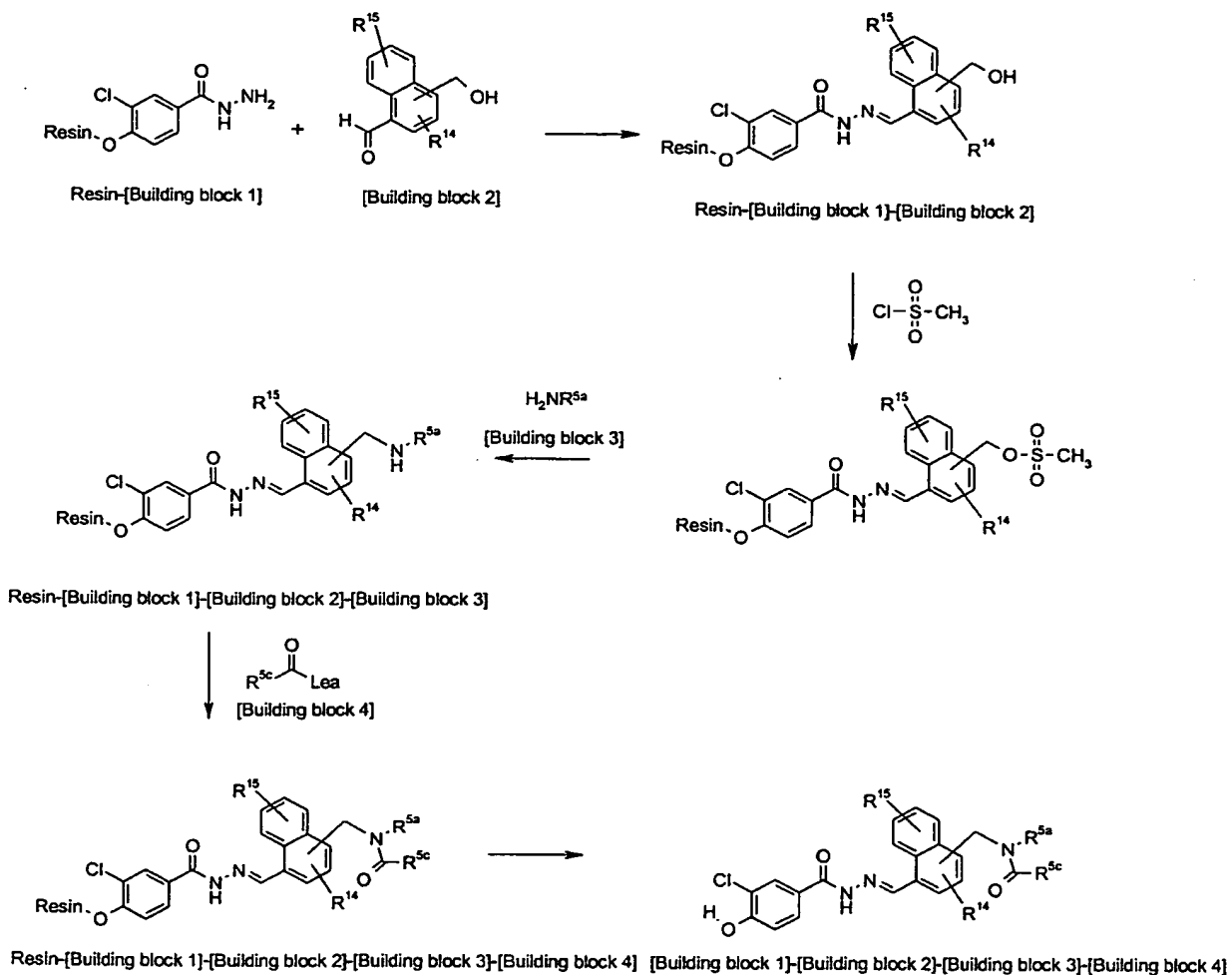
[Building block 1]—[Building block 2]—[Building block 3]—[Building block 4].

5 The following compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1]-[Building block 2] was done manually, whereas the attachment of [Building block 3], attachment of [Building block 4] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

10 The starting resin, Resin-[Building block 1], was prepared as described above.

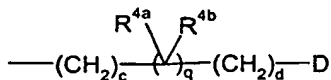
The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

15 All compounds are based on successive attachment of [Building block 2] and [Building block 3] to Resin-[Building block 1] in a combinatorial way using a nucleophilic substitution reaction followed by an acylation reaction attaching [Building block 4] according to the following formulae, which are included in the general formula II:



wherein  $\text{R}^{5a}$ ,  $\text{R}^{14}$ ,  $\text{R}^{15}$  are as defined for formula I and  $\text{R}^{5c}$  is

5

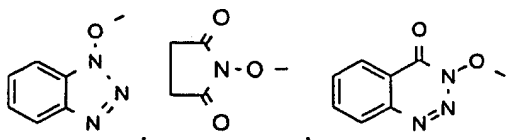


where  $\text{R}^{4a}$ ,  $\text{R}^{4b}$ ,  $c$ ,  $q$ ,  $d$ , and  $D$  are as defined for formula I or

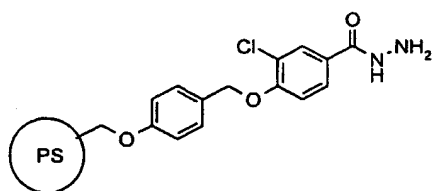
-D' where -D' is defined as a subset of -D that contains an activated carboxylic acid capable of reacting as an electrophile and

10

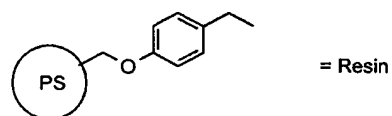
Lea is a leaving group such as chloro, bromo, iodo, carboxylate,



The following resin, here depicted as Resin-[Building block 1] was used:



where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:

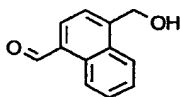


5

The following building blocks were used:

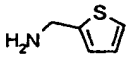
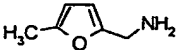
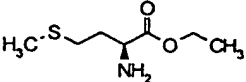
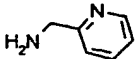
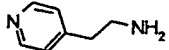
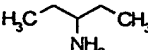
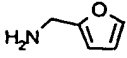
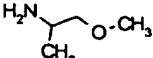


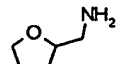
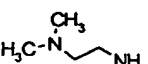



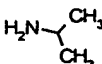
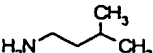



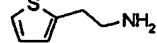
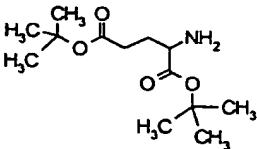
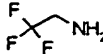
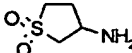
[Building block 2]:

4-Hydroxymethylnaphthalene-1-carbaldehyde

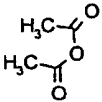
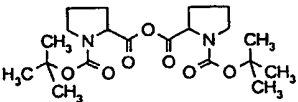


10

## [Building block 3]:

<b>2-Thiophenemethylamine</b> 	<b>5-Methyl-2-furanmethylamine</b> 	<b>L-Methionine ethyl ester</b> 
<b>2-(Aminomethyl)pyridine</b> 	<b>4-(2-Aminoethyl)pyridine</b> 	<b>3-Aminopentane</b> 
<b>Furfurylamine</b> 	<b>2-Methoxyisopropylamine</b> 	<b>Cyclopropylamine</b> 
<b>Glycine</b> 	<b>2-Furanylmethylamine</b> 	<b>N,N-Dimethylethylenedi-amine</b> 
<b>Ethylamine</b> 	<b>Methylamine</b> 	<b>Propylamine</b> 
<b>Isopropylamine</b> 	<b>Isopentylamine</b> 	<b>Cyclopentylamine</b> 
<b>Cyclopropylmethylamine</b> 	<b>Cyclobutylamine</b> 	<b>Thiophene-2-ethylamine</b> 
<b>Glutamic Acid di tert butyle-ster</b> 	<b>2,2,2-Trifluoroethylamine</b> 	<b>Tetrahydro-3-thiophenamine 1,1-dioxide</b> 

[Building block 4]:

Acetic anhydride	N- <i>tert</i> Butoxycarbonyl-proline anhydride
	

Preparation of resin-[Building block 1]:

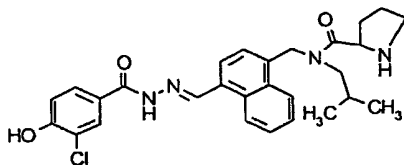
5

This resin was prepared as described above.

Preparation of resin-[Building block 1]-[Building block 2]:

10 This resin was prepared as described above.

## EXAMPLE 876:

N-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]naphthylmethyl}-N-isobutylprolinamide

15

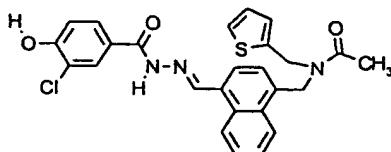
The resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthyl-methylene)hydrazide (resin-[Building block 1]-[Building block 2]) (50 mg, ~ 50  $\mu$ moles) was swelled in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) for 15 min, then washed twice with  $\text{CH}_2\text{Cl}_2$  (0.5 mL). 0.4 mL  $\text{CH}_2\text{Cl}_2$  and 0.4 mL diisopropylethylamine were subsequently added and the suspension was cooled to 0  $^\circ\text{C}$ . Methanesulfonylchloride (0.1 mL) was dissolved in  $\text{CH}_2\text{Cl}_2$  (0.3 mL) and added to the suspension. The mixture was allowed to react at 0  $^\circ\text{C}$  for 30 min, then at 25  $^\circ\text{C}$  for 1 hour. The resin was isolated by filtration and washed with  $\text{CH}_2\text{Cl}_2$  (2 x 0.5 mL) and DMSO (0.5 mL). 0.5 mL DMSO was added to the resin followed by isobutylamine (50  $\mu\text{L}$ )

and diisopropylethylamine (100  $\mu$ L). The mixture was shaken at 25 °C for 16 hours. The solvent was removed by suction and the resin was washed with DMSO (2 x 0.5 mL) and THF (3 x 0.5 mL). To a solution of N-*tert*-butoxycarbonyl-proline (46 mg, 0.21 mmol) in THF (0.5 mL) was added diisopropylcarbodiimide (16  $\mu$ L, 0.2 mmol). This solution was allowed to react at 25 °C for 10 minutes and then added to the resin. The suspension was shaken at 25 °C for 16 hours after which the resin was isolated by suction and washed with THF (3 x 0.5 mL), DMF (3 x 0.5 mL) THF (3 x 0.5 mL), CH<sub>3</sub>OH (0.5 mL), CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL), CH<sub>3</sub>OH (0.5 mL), CH<sub>2</sub>Cl<sub>2</sub> (4 x 0.5 mL). The compound was cleaved from the resin by shaking for 1 hour at 25 °C with a 50% solution of trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was filtered and the resin was extracted with acetonitrile (1 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of CH<sub>3</sub>OH (0.5 mL) and acetonitrile (0.5 mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD B):  $R_t$  = 3.90 min;  $m/z$  = 507 (M+1).

#### EXAMPLE 877:

3-Chloro-4-hydroxybenzoic acid ((4-(4-trifluoromethoxybenzylamino)methyl)naphthylmethylene)hydrazide



20

Resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide (resin-[building block 1]-[building block 2]) (50 mg) was swelled in a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and N-methyl-2-pyrrolidone (0.5 mL) for 15 minutes and then washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 0.5 mL). 800  $\mu$ L of a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and diisopropylethylamine was added to the resin which subsequently was cooled to -3 °C. A solution of 100  $\mu$ L methanesulfonylchloride dissolved in 300  $\mu$ L was added and allowed to react at -3 °C for 30 minutes then at 25 °C for 1 hour. Filtration of the resin was followed by washing with CH<sub>2</sub>Cl<sub>2</sub> (2 x 1 mL) and N-methyl-2-pyrrolidone (2 x 0.5 mL). 600  $\mu$ L of a solution of 4-trifluoromethoxybenzylamine (45.8 mg, 0.24 mmol, 0.4M) and KI (10 mg, 0.06 mmol, 0.1M) in N-methyl-2-pyrrolidone (0.5 mL) and

diisopropylethylamine (0.1 mL) was added and allowed to react at 25 °C for 16 hours. The resin was isolated by filtration and washed successively with N-methyl-2-pyrrolidone (5 x 0.5 mL) and THF (3 x 0.5 mL). 600 µL of a solution of acetic anhydride (120 µL, 130 mg, 1.27 mmol) in THF (480 µL) was added to the resin. The mixture was allowed to react at 25 °C for 16 hr. The resin was filtered and washed successively with THF (2 x 0.8 mL), CH<sub>3</sub>OH (0.8 mL), CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL), CH<sub>3</sub>OH (0.8 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 x 0.8 mL). The compound was cleaved from the resin by shaking for 1 hour at 25 °C with a solution of 50% trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was filtered and the resin was extracted with acetonitrile (1 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of CH<sub>3</sub>OH (0.5 mL) and acetonitrile (0.5 mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD B): R<sub>t</sub> = 6.42 min; m/z = 492 (M+1)

#### EXAMPLES 878 TO 881:

A library of compounds of all the possible combinations of the above listed building blocks ([building block 1], [building block 2], [building block 3] and acetic anhydride as [building block 4]) was prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model 384 HTS using the following ChemFile to control the operation of the synthesizer. The compounds are all expected to be present in the respective wells.

A suspension of the resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethyl-naphthylmethylene)hydrazide (resin-[building block 1]-[building block 2]) (50 mg) in a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and N-methyl-2-pyrrolidone (0.5 mL) is equally distributed in the wells in the synthesizer prior to the initialization of the device.

ChemFile C:\ACT\_1328\MAIN.CHM

30

1 REM Nucleophilic displacement of benzylic alcohol

2 REM via mesylation

3

4

5 REM Dipense resin bound benzylic alchohol to wells  
6  
7  
8 REM Setup Diluter1=DCM, D2=NMP (N-methyl-2-pyrrolidone), D3=NMP, D4=DCM  
5 9 REM Adjust pressure  
10 REM Add 100 mL DIEA/DCM 1:1 mixture to Reagent1  
11 REM Add 70 mL MsCl/DCM 1:3 mixture to Reagent2  
12 REM Add 100 mL TFA/DCM 1:1 mixture to Reagent3  
13 REM Add 100 mL CH3CN to Reagent4  
10 14 REM Nitrogen for cooling  
15  
16 Pause  
17 REM Initialising...  
18  
15 19 REM Subroutine Empty1\_72\_3min is called twice to remove DCM/NMP from dispensed resin  
20 Go to ChemFile MTY72\_3M.CHM, line 1  
21 Go to ChemFile MTY72\_3M.CHM, line 1  
22  
20 23 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and with Flush Diluter 4  
24  
25 REM Washing with DCM, 3 times  
26 Dispense System Fluid Disdu1\_4\* 500ul to RB1\_1to96[1-72]  
25 27 Mix "RB1\_1to96" for 3.00 minutes at 300 rpm(s) and wait.  
28 REM Subroutine Empty1\_72\_3min  
29 Go to ChemFile MTY72\_3M.CHM, line 1  
30 Repeat from step 26, 2 times  
31  
30 32 REM Adding DCM/DIEA mixture from Reagent1  
33 Transfer 800ul from REAGENT\_1[1](DCM/DIEA) to RB1\_1to96[1-72] using Flush Diluter1  
34 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
35 Set Temperature of rack "RB1\_1to96" to -3.0 degrees Celsius and wait for Temperature to reach setpoint  
35 36 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
37 REM Ensure complete cooling  
38 Wait for 15.000 minute(s)  
39  
40 REM Adding mesylchloride  
40 41 Transfer 400ul from REAGENT\_2[1](MsCl/DCM) to RB1\_1to96[1-72] using Flush Diluter1  
42 REM Reacts 30 min @ -3 °C  
43 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
44 Wait for 4.000 minute(s)  
45 Repeat from step 43, 5 times  
45 46  
47 REM Reacts 60 min @ 25 C  
48 Set Temperature of rack "RB1\_1to96" to 25.0 degrees Celsius and wait for Temperature to reach setpoint  
49 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.

50 Wait for 4.000 minute(s)  
51 Repeat from step 46, 11 times  
52  
53 REM Subroutine Empty1\_72\_3min  
5 54 Go to ChemFile MTY72\_3M.CHM, line 1  
55  
56 REM Initiate washing procedure, 2XDCM  
57 Dispense System Fluid Disdu1\_4\* 1000ul to RB1\_1to96[1-72]  
58 Mix "RB1\_1to96" for 3.00 minutes at 300 rpm(s) and wait.  
10 59 Go to ChemFile MTY72\_3M.CHM, line 1  
60 Repeat from step 57, 1 times  
61  
62 REM NMP wash  
63  
15 64 Dispense System Fluid Disdu2\_3\* 500ul to RB1\_1to96[1-72]  
65 Mix "RB1\_1to96" for 5.00 minutes at 300 rpm(s) and wait.  
66 Go to ChemFile MTY72\_3M.CHM, line 1  
67  
68 Go to ChemFile MTY72\_3M.CHM, line 1  
20 69 Repeat from step 64, 1 times  
70  
71 REM Make sure that nucleophiles are dissolved and ready for addition  
72 Pause  
73  
25 74 Dispense Sequence C:\ACT\_1328\R2-A.DSP with 600ul to RB1\_1to96 rack using Flush  
Diluter 2  
75 REM Nucleophiles react @ 25 C for 16 hr  
76 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
77 Wait for 4.000 minute(s)  
30 78 Repeat from step 76, 11 times  
79 Repeat from step 76, 15 times  
80  
81 REM End of nucleophilic substitution reaction  
82 Go to ChemFile MTY72\_3M.CHM, line 1  
35 83 Go to ChemFile MTY72\_3M.CHM, line 1  
84  
85 REM Commence washing procedure  
86 Dispense System Fluid Disdu2\_3\* 500ul to RB1\_1to96[1-72]  
87 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
40 88 Go to ChemFile MTY72\_3M.CHM, line 1  
89 Go to ChemFile MTY72\_3M.CHM, line 1  
90 Repeat from step 86, 4 times  
91  
92 REM Change systemfluids:  
45 93 REM \* Diluter2: THF  
94 REM \* Diluter3: MeOH  
95 Pause  
96

- 97 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and Flush Diluter 4  
98 REM THF wash 3 times  
99 Dispense System Fluid Flush Diluter 2 500ul to RB1\_1to96[1-72]  
5 100 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
101 Go to ChemFile MTY72\_3M.CHM, line 1  
102 Go to ChemFile MTY72\_3M.CHM, line 1  
103 Repeat from step 99, 2 times  
104 Go to ChemFile Acylation.CHM, line 1  
10 105 Go to ChemFile WASH.CHM, line 1  
106 Go to ChemFile Cleavage.CHM, line 1  
107 REM The End

The following chemfile is called to acylate the amines:

15

ChemFile C:\ACT\_1328\Acetyl.CHM

- 1 REM Acetylation procedure  
2 REM Charge REAGENT\_5 with 100 mL Acetic anhydride/THF 1:4 v/v  
20 3 REM \* Diluter2: THF  
4 REM Addition of acylation reagent  
5 Dispense Sequence C:\R3-A.DSP with 600 µL to RB1to96 rack using Flush Diluter 2  
6 Mix for 1.00 minutes at 300 rpm(s)  
7 Wait for 5.000 minute(s)  
25 8 Repeat from step 6, 60 times  
9 Go to ChemFile MTY72\_3M.CHM, line 1  
10 Go to ChemFile MTY72\_3M.CHM, line 1  
11 Return

- 30 The following chemfile is called to wash the resin bound products:

ChemFile C:\ACT\_1328\WASH.CHM

- 1 REM Washing procedure  
35 2 REM Systemfluids:  
3  
4 REM \* Diluter2: THF  
5 REM \* Diluter3: MeOH  
6  
40 7 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and Flush Diluter 4  
8 REM THF wash 3 times  
9 Dispense System Fluid Flush Diluter 2 800ul to RB1\_1to96[1-72]  
10 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.

- 11 Go to ChemFile MTY72\_3M.CHM, line 1  
12 Go to ChemFile MTY72\_3M.CHM, line 1  
13 Repeat from step 9, 2 times  
14  
5 15 REM Alternating MeOH/DCM wash, 2 cycles  
16 Dispense System Fluid Flush Diluter 3 800ul to RB1\_1to96[1-72]  
17 Mix "RB1\_1to96" for 3.00 minutes at 300 rpm(s) and wait.  
18 Go to ChemFile MTY72\_3M.CHM, line 1  
19  
10 20 Dispense System Fluid Disdu1\_4\* 800ul to RB1\_1to96[1-72]  
21 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
22 Go to ChemFile MTY72\_3M.CHM, line 1  
23 Go to ChemFile MTY72\_3M.CHM, line 1  
24  
15 25 Repeat from step 16, 1 times  
26  
27 Dispense System Fluid Disdu1\_4\* 800ul to RB1\_1to96[1-72]  
28 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.  
29 Go to ChemFile MTY72\_3M.CHM, line 1  
20 30 Repeat from step 117, 1 times  
31  
32 REM Washing procedure has ended  
33 Return

- 25 The following chemfile is called to cleave the products from the resin:

ChemFile C:\ACT\_1328\Cleavage.CHM

- 1 REM Setup for cleavage:  
30 2 REM \* Cleavage vials  
3 REM \* Lower pressure  
4 REM \* Add 100 mL TFA/DCM 1:1 mixture to Reagent3  
5 REM \* Add 100 mL CH3CN to Reagent4  
6 Pause  
35 7  
8 REM Adding cleavage solution, 1hr  
9 Transfer 1000ul from REAGENT\_3[1](TFA/DCM) to RB1\_1to96[1-72] using Flush Diluter1  
10 Mix "RB1\_1to96" for 1.00 minutes at 300 rpm(s) and wait.  
11 Wait for 4.000 minute(s)  
40 12 Repeat from step 133, 11 times  
13 REM PULSE EMPTY!  
14 Go to ChemFile PULSEMP1.CHM, line 1  
15  
16 REM Washing with CH3CN  
45 17 Transfer 500ul from REAGENT\_4[1](CH3CN) to RB1\_1to96[1-72] using Flush Diluter1  
18 Mix "RB1\_1to96" for 10.00 minutes at 300 rpm(s) and wait.

19 REM PULSE EMPTY!  
20 Go to ChemFile PULSEMP1.CHM, line 1  
21 Return

- 5 The following chemfile is called to empty the wells of the reaction block.:

ChemFile C:\ACT\_1328\MTY72\_3M.CHM Page 1

- 10 1 REM Subroutine Empty1\_72\_3min  
2 Empty RB1\_1to96 for 5.000 minute(s)  
3 Return

The following chemfile is called to empty the wells of the reaction block into the cleavage vials containing the final product in a controlled manner.

15

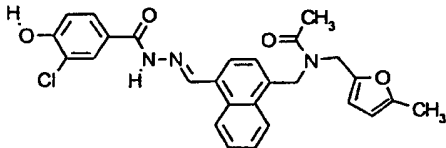
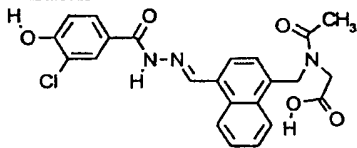
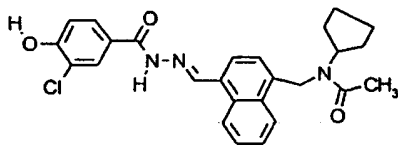
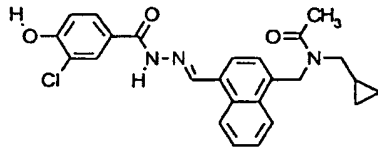
ChemFile C:\ACT\_1328\PULSEMP1.CHM Page 1

- 20 1 Empty RB1\_1to96 for 1 second(s)  
2 Wait for 4 second(s)  
3 Repeat from step 1, 11 times  
4 Empty RB1\_1to96 for 5.000 minute(s)  
5 Return

- 25 Dispense sequence C:\ACT\_1328\R2-A.DSP is a subroutines that control the combinatorial addition of the amines into the reaction block in the synthesiser.

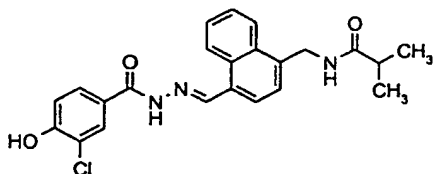
Dispense sequence C:\ACT\_1328\R3-A.DSP is a subroutines that control the combinatorial addition of the acylating agents into reaction block in the synthesiser.

- 30 Examples of compounds from this library were characterised by HPLC-MS (molecular mass & retention time) including the following examples 878 to 881.

Ex No.	Structure	HPLC-MS (METHOD B) m/z (M+1)	HPLC-MS (METHOD B) R <sub>t</sub> (minutes)
878		490	6.22
879		454	1.05
880		464	6.33
881		450	5.30

## EXAMPLE 882:

N-{4-[3-chloro-4-hydroxybenzoyl]-hydrazonomethyl}-1-naphthyl)methyl iso-propyl amide



5

Preparation of *N*-4-Formylnaphthylmethyl isopropyl amide:

A mixture of 4-bromomethyl-1-naphthaldehyde ethyleneacetal (447 mg, 1.52 mmol) and  $\text{NaN}_3$  (221 mg, 3.4 mmol) in 10 mL DMF was warmed up to 100 °C and stirred for 30 min. Solution turned orange. The reaction was filtered and the clear solution was concentrated to 391 mg of yellow oil. This oil (249 mg) together with triphenylphosphine (260 mg, 0.99 mmol) was dissolved in 10 mL of THF. The reaction mixture was left overnight followed by the addition of water. Ninhydrin test revealed the formation of an amine. This amine was extracted into ethyl acetate layer, dried to give an oil. This oil was dissolved in  $\text{CH}_2\text{Cl}_2$ , EDC, DMAP and 2-methylpropionic acid were added. The reaction mixture was left for 2 days. Column chromatography eluted with ethyl acetate afforded the amide. Deprotection of di-ethyleneacetal was achieved by 10% HCl in THF to give the title compound (50 mg).

20

The title compound was prepared similarly as described above.

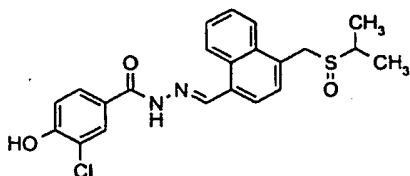
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): d 1.2 (d, 6H), 2.4 (m, 1H), 4.9 (d, 2H), 6.1 (b, 1H), 7.5 (d, 1H), 7.6 (m, 2H), 7.8 (d, 1H), 8.0 (d, 1H), 9.2 (d, 1H), 10.3 (s, 1H).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): d 1.0 (d, 6H), 2.4 (m, 1H), 4.7 (s, 2H), 7.0 (d, 1H), 7.4 (d, 1H), 7.6 (m, 2H), 7.7 (d, 1H), 7.8 (d, 1H), 7.9 (s, 1H), 8.1 (d, 1H), 8.3 (s, 1H), 8.8 (d, 1H), 9.0 (s, 1H), 10.9 (s, 1H), 11.7 (s, 1H); ms (APCI negative); 422.

25

## EXAMPLE 883:

4-[3-chloro-4-hydroxybenzoyl]-hydrazonomethyl-1-naphthylmethyl iso-propylsulfoxide



#### 4-Ethylenecetal-4-formyl-naphthylmethyl *iso*-propylthioether:

A mixture of 4-bromomethyl naphthaldehyde ethylenecetal (232 mg, 0.79 mmol) and *iso*-propyl thioalcohol (0.08 mL, 0.81 mmol) and 0.12 mL of triethylamine was left at room temperature for 12 h. The reaction mixture was concentrated and the residue was purified by column chromatography eluted with ethyl acetate /hexane (1/5) to afford 93 mg of the desired product as pale radish oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.3 (d, 6H), 2.9 (m, 1H), 4.2 (m, 6H), 6.5 (s, 1H), 7.4 (d, 1H), 7.6 (m, 2H), 7.7 (d, 1H), 8.2 (m, 1H).

#### 4-Ethylenecetal-naphthylmethyl *iso*-propylsulfoxide:

To a mixture of the above 4-ethylenecetal-naphthylmethyl *iso*-propylthioether (79 mg, 0.27 mmol) in 5 mL of dichloromethane at -78 °C was added *m*-chloro perbenzoic acid (82 mg, 55% purity, 0.28 mmol). The reaction mixture was left for 1 hour and 40 min. Then, NaHSO<sub>3</sub> solution was added followed by NaHCO<sub>3</sub>. The mixture was extracted with water and dichloromethane. The organic layer was combined and dried over MgSO<sub>4</sub>. Solvent was removed and the residue was purified by column chromatography eluted with ethyl acetate to yield 56 mg of desired product as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.3 (d, 3H), 1.4 (d, 3H), 2.7 (m, 1H), 4.2 (m, 4H), 4.4 (dd, 2H), 6.5 (s, 1H), 7.5 (d, 1H), 7.6 (m, 2H), 7.7 (d, 1H), 8.1 (m, 1H), 8.2 (m, 1H). This compound was hydrolyzed in aqueous 10% HCl in THF for 1 hr to give the corresponding aldehyde.

#### 4-[3-chloro-4-hydroxybenzoyl]-hydrazonomethyl]-1-naphthylmethyl *iso*-propylsulfoxide:

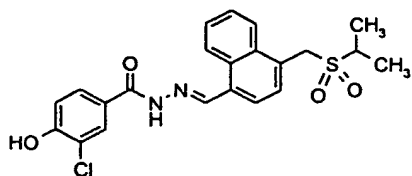
The title compound was prepared similarly as described above.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): d 1.3 (dd, 6H), 3.0 (m, 1H), 4.3 (d, 1H), 4.7 (d, 1H), 7.1 (d, 1H), 7.6 (m, 3H), 7.8 (d, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 8.2 (d, 1H), 8.8 (d, 1H), 9.1 (s, 1H), 11.0 (s, 1H), 11.8 (s, 1H); ms (APCI negative); 427, 337.

5

## EXAMPLE 884:

4-[3-chloro-4-hydroxybenzoyl]-hydrazonomethyl]-1-naphthylmethyl iso-propylsulfone



10

Similarly, the title compound was prepared.

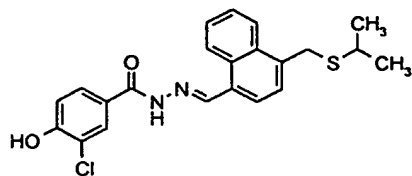
<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): d 1.3 (d, 6H), 3.4 (m, 1H), 5.0 (s, 2H), 7.0 (d, 1H), 7.6 (m, 3H), 7.7 (d, 1H), 7.9 (d, 2H), 8.2 (d, 1H), 8.7 (d, 1H), 9.0 (s, 1H), 10.9 (s, 1H), 11.8 (s, 1H); ms (APCI negative); 443, 336.

15

## EXAMPLE 885:

4-[3-chloro-4-hydroxybenzoyl]-hydrazonomethyl]-1-naphthylmethyl iso-propylsulfide

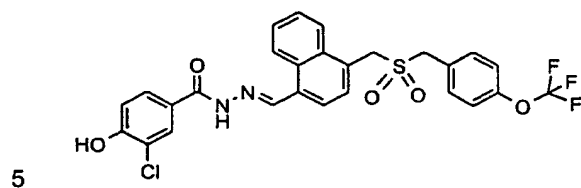
20



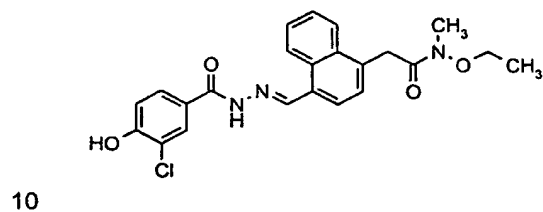
Similarly, the title compound was prepared.

Further examples of the invention are the following compounds:

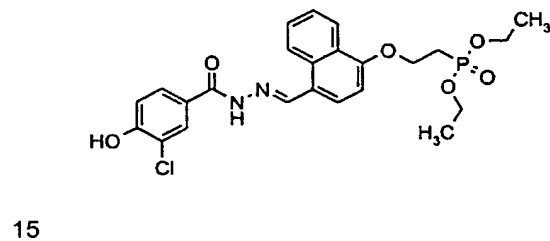
EXAMPLE 886:



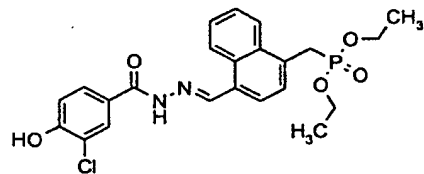
EXAMPLE 887:



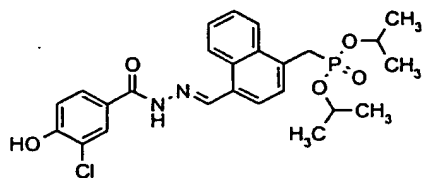
EXAMPLE 888:



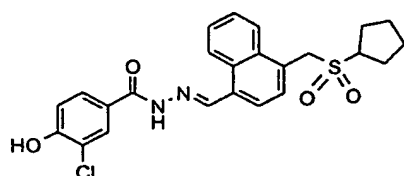
EXAMPLE 889:



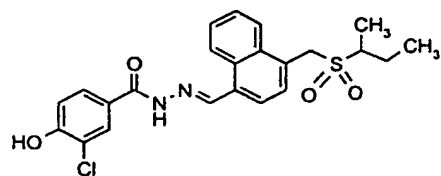
## EXAMPLE 890:



## 5 EXAMPLE 891:

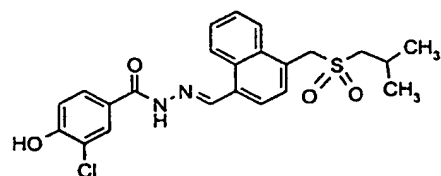


## EXAMPLE 892:



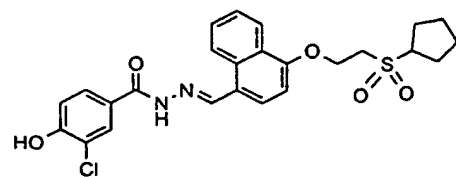
10

## EXAMPLE 893:



15

## EXAMPLE 894:



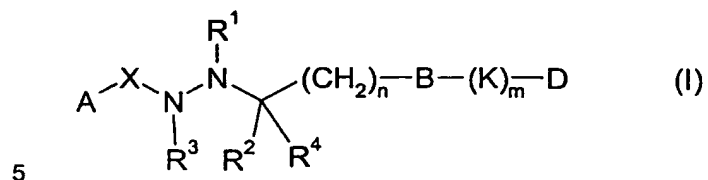
20

It should be apparent from the foregoing that other starting materials and other intermediate compounds can be substituted in the above procedures to prepare all of the compounds of the invention. The methods disclosed herein are based on established chemical techniques, as  
5 will be apparent to those skilled in the art, and therefore all of the compounds of the invention are broadly enabled by the preceding disclosure.

Accordingly, the invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all re-  
10 spects only as illustrative and not restrictive, and the scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All modifications which come within the meaning and range of the lawful equivalency of the claims are to be embraced within their scope.

## Claims

1. A compound of the general formula I:



wherein:

10  $\text{R}^1$  and  $\text{R}^2$  independently are hydrogen or lower alkyl or together form a valence bond;

$\text{R}^3$  and  $\text{R}^4$  independently are hydrogen or lower alkyl;

$n$  is 0, 1, 2 or 3;

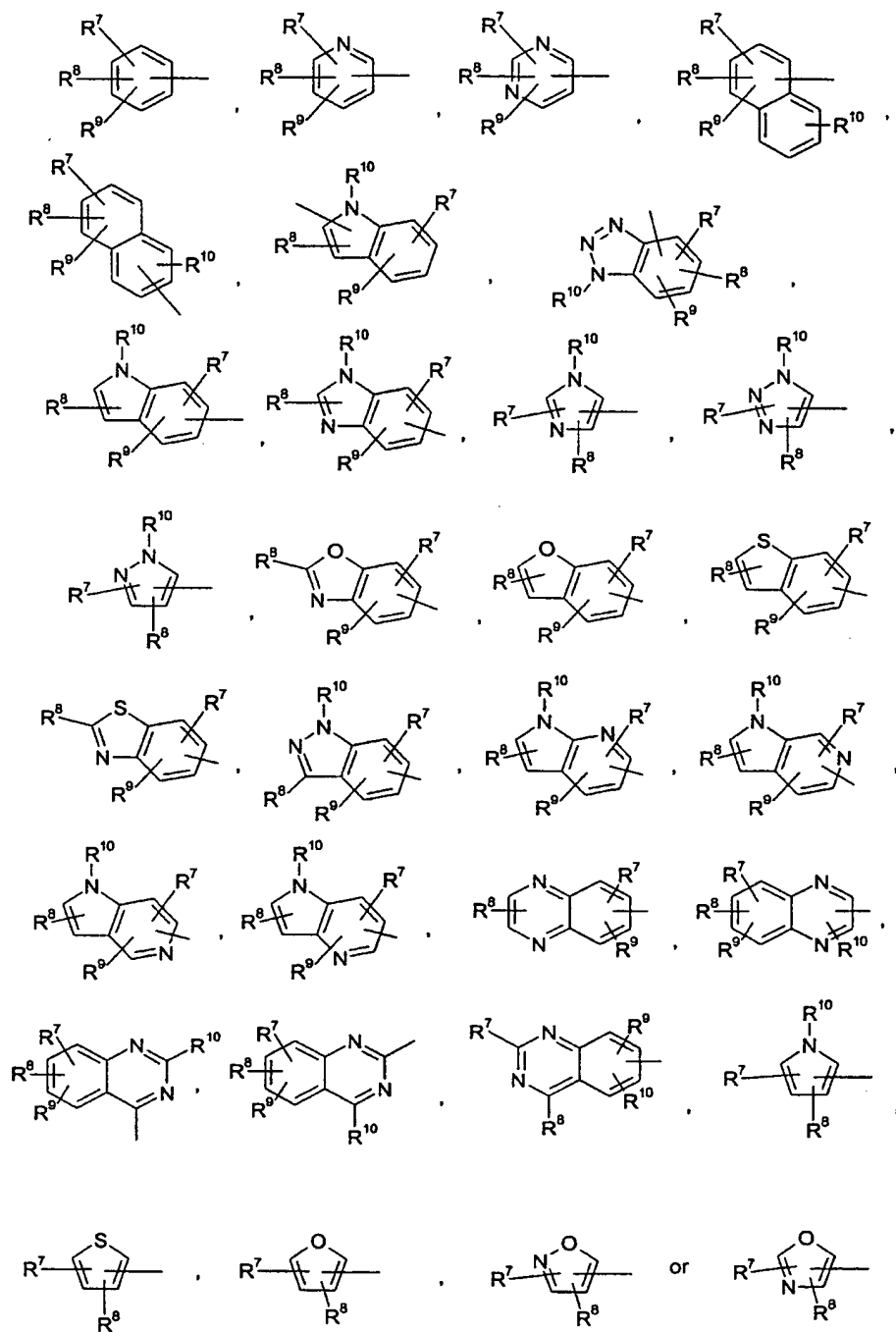
15  $m$  is 0 or 1;

$\text{X}$  is  $>\text{C}=\text{O}$ ,  $>\text{C}=\text{S}$ ,  $>\text{C}=\text{NR}^5$  or  $>\text{SO}_2$ ;

20 wherein  $\text{R}^5$  is hydrogen, lower alkyl, aryl-lower alkyl or  $-\text{OR}^6$ ;

wherein  $\text{R}^6$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

$\text{A}$  is



wherein:

$R^7$  is hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -OCH<sub>2</sub>CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup> or -OSO<sub>2</sub>CF<sub>3</sub>;

- 5  $R^8$  and  $R^9$  independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>11</sup>, -NR<sup>11</sup>R<sup>12</sup>, lower alkyl, aryl, -SCF<sub>3</sub>, -SR<sup>11</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OSO<sub>2</sub>R<sup>11</sup>, -CONR<sup>11</sup>R<sup>12</sup>, -CH<sub>2</sub>OR<sup>11</sup>, -CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, -OCOR<sup>11</sup>, -CO<sub>2</sub>R<sup>13</sup> or -OSO<sub>2</sub>CF<sub>3</sub>, or  $R^8$  and  $R^9$  together form a bridge -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;

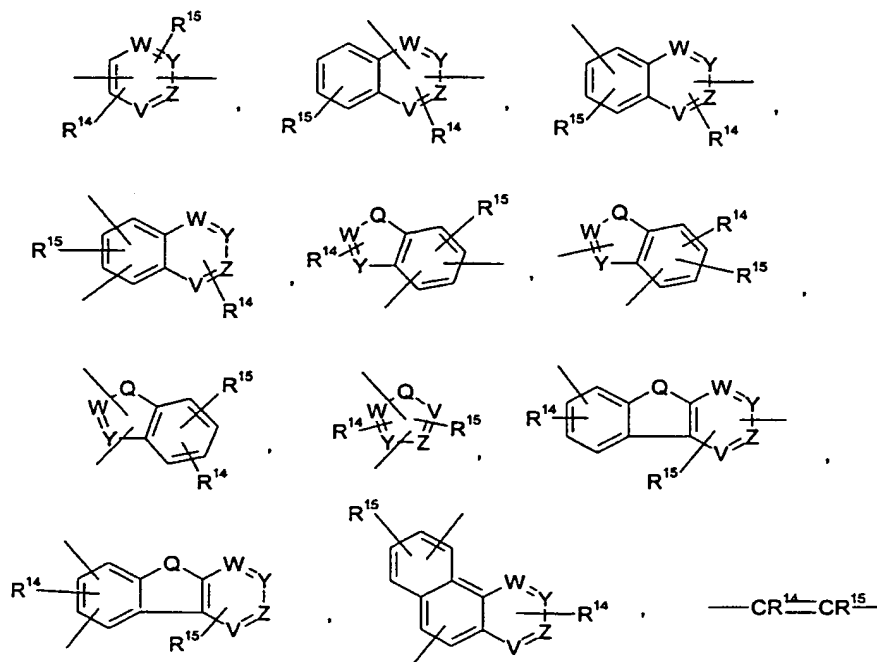
- 10 wherein  $R^{11}$  and  $R^{12}$  independently are hydrogen, -COR<sup>13</sup>, -SO<sub>2</sub>R<sup>13</sup>, lower alkyl or aryl;

wherein  $R^{13}$  is hydrogen, lower alkyl, aryl-lower alkyl or aryl; and

$R^{10}$  is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

15

B is



or a valence bond;

- 20 wherein:

$R^{14}$  and  $R^{15}$  independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -O(CH<sub>2</sub>)<sub>l</sub>CF<sub>3</sub>, -NO<sub>2</sub>,  
 -OR<sup>16</sup>, -NR<sup>16</sup>R<sup>17</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>16</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>16</sup>R<sup>17</sup>, -(CH<sub>2</sub>)<sub>l</sub>CONR<sup>16</sup>R<sup>17</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CONR<sup>16</sup>R<sup>17</sup>, -(CH<sub>2</sub>)<sub>l</sub>COR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>COR<sup>16</sup>,  
 5 -(CH<sub>2</sub>)<sub>l</sub>OR<sup>16</sup>, -O(CH<sub>2</sub>)<sub>l</sub>OR<sup>16</sup>, -(CH<sub>2</sub>)<sub>l</sub>NR<sup>16</sup>R<sup>17</sup>, -O(CH<sub>2</sub>)<sub>l</sub>NR<sup>16</sup>R<sup>17</sup>, -OCOR<sup>16</sup>, -CO<sub>2</sub>R<sup>18</sup>,  
 -O(CH<sub>2</sub>)<sub>l</sub>CO<sub>2</sub>R<sup>18</sup>, -O(CH<sub>2</sub>)<sub>l</sub>CN, -O(CH<sub>2</sub>)<sub>l</sub>Cl, or  $R^{14}$  and  $R^{15}$  together form a bridge -O(CH<sub>2</sub>)<sub>l</sub>O- or  
 -(CH<sub>2</sub>)<sub>l</sub>-;

wherein  $l$  is 1, 2, 3 or 4;

10

$R^{16}$  and  $R^{17}$  independently are hydrogen, -COR<sup>18</sup>, -SO<sub>2</sub>R<sup>18</sup>, lower alkyl, aryl, or  $R^{16}$  and  $R^{17}$   
 together form a cyclic alkyl bridge containing from 2 to 7 carbon atoms;

wherein  $R^{18}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

15

W is -N= or -CR<sup>19</sup>=;

Y is -N= or -CR<sup>20</sup>=;

20

Z is -N= or -CR<sup>21</sup>=;

V is -N= or -CR<sup>22</sup>=; and

Q is -NR<sup>23</sup>-, -O- or -S-;

25

wherein:

$R^{19}$ ,  $R^{20}$ ,  $R^{21}$  and  $R^{22}$  independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>,  
 -NO<sub>2</sub>, -OR<sup>24</sup>, -NR<sup>24</sup>R<sup>25</sup>, lower alkyl, aryl, aryl-lower alkyl, -SCF<sub>3</sub>, -SR<sup>24</sup>, -CHF<sub>2</sub>, -OCHF<sub>2</sub>,  
 30 -OCF<sub>2</sub>CHF<sub>2</sub>, -OSO<sub>2</sub>CF<sub>3</sub>, -CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -OCH<sub>2</sub>CONR<sup>24</sup>R<sup>25</sup>, -CH<sub>2</sub>OR<sup>24</sup>,  
 -CH<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, -OCOR<sup>24</sup> or -CO<sub>2</sub>R<sup>24</sup>, or  $R^{19}$  and  $R^{20}$ ,  $R^{20}$  and  $R^{21}$ , or  $R^{21}$  and  $R^{22}$  together form a  
 bridge -OCH<sub>2</sub>O-;

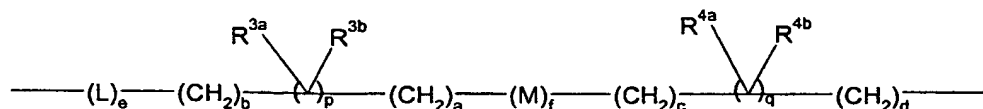
wherein  $R^{24}$  and  $R^{25}$  independently are hydrogen,  $-\text{COR}^{26}$ ,  $-\text{SO}_2\text{R}^{26}$ , lower alkyl, aryl or aryl-lower alkyl;

wherein  $R^{26}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

5

$R^{23}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



10

wherein:

$R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$  and  $R^{4b}$  independently are hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^{24a}$ ,  $-\text{NR}^{24a}\text{R}^{25a}$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{SCF}_3$ ,  $-\text{SR}^{24a}$ ,  $-\text{CHF}_2$ ,  $-\text{OCHF}_2$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{OSO}_2\text{CF}_3$ ,  $-\text{CONR}^{24a}\text{R}^{25a}$ ,  $-\text{CH}_2\text{CONR}^{24a}\text{R}^{25a}$ ,  $-\text{OCH}_2\text{CONR}^{24a}\text{R}^{25a}$ ,  $-\text{CH}_2\text{OR}^{24a}$ ,  $-\text{CH}_2\text{NR}^{24a}\text{R}^{25a}$ ,  $-\text{OCOR}^{24a}$  or  $-\text{CO}_2\text{R}^{24a}$ ;

15

wherein  $R^{24a}$  and  $R^{25a}$  independently are hydrogen,  $-\text{COR}^{26a}$ ,  $-\text{SO}_2\text{R}^{26a}$ , lower alkyl, aryl or aryl-lower alkyl;

20

wherein  $R^{26a}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

or

$R^{3a}$  and  $R^{3b}$ ,  $R^{4a}$  and  $R^{4b}$ , or  $R^{3a}$  and  $R^{4b}$  together form a bridge  $-(\text{CH}_2)_i$ ;

25

wherein  $i$  is 1, 2, 3 or 4;

$a$ ,  $b$ ,  $c$  and  $d$  independently are 0, 1, 2, 3 or 4;

30

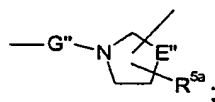
$e$ ,  $f$  and  $p$  independently are 0 or 1;

q is 0, 1 or 2; and

L and M independently are

- 5 -O-, -S-, -CH=CH-, -C≡C-, -NR<sup>5a</sup>-, -CH<sub>2</sub>NR<sup>5a</sup>-, -CO-, -OCO-, -COO-, -CONR<sup>5a</sup>-, -CONR<sup>5b</sup>-,  
 -NR<sup>5a</sup>CO-, -SO-, -SO<sub>2</sub>-, -OSO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>5a</sup>-, -NR<sup>5a</sup>SO<sub>2</sub>-, -NR<sup>5a</sup>CONR<sup>5b</sup>-, -CONR<sup>5a</sup>NR<sup>5b</sup>-,  
 -NR<sup>5a</sup>CSNR<sup>5b</sup>-, -OCONR<sup>5b</sup>-, -CH<sub>2</sub>CONR<sup>5b</sup>-, -OCH<sub>2</sub>CONR<sup>5b</sup>-,

-P(O)(OR<sup>5a</sup>)O-, -NR<sup>5a</sup>C(O)O- or



- 10 wherein R<sup>5a</sup> and R<sup>5b</sup> independently are hydrogen, lower alkyl, -OH, -(CH<sub>2</sub>)<sub>k</sub>-OR<sup>6a</sup>, -COR<sup>6a</sup>,  
 -(CH<sub>2</sub>)<sub>k</sub>-CH(OR<sup>6a</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>k</sub>-CN, -(CH<sub>2</sub>)<sub>k</sub>-NR<sup>6a</sup>R<sup>6b</sup>, aryl, aryl-lower alkyl, -(CH<sub>2</sub>)<sub>g</sub>-COOR<sup>43</sup> or -  
 (CH<sub>2</sub>)<sub>g</sub>-CF<sub>3</sub>;

wherein k is 1, 2, 3 or 4;

- 15 R<sup>6a</sup> and R<sup>6b</sup> independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl;

g is 0, 1, 2, 3 or 4;

R<sup>43</sup> is hydrogen or lower alkyl;

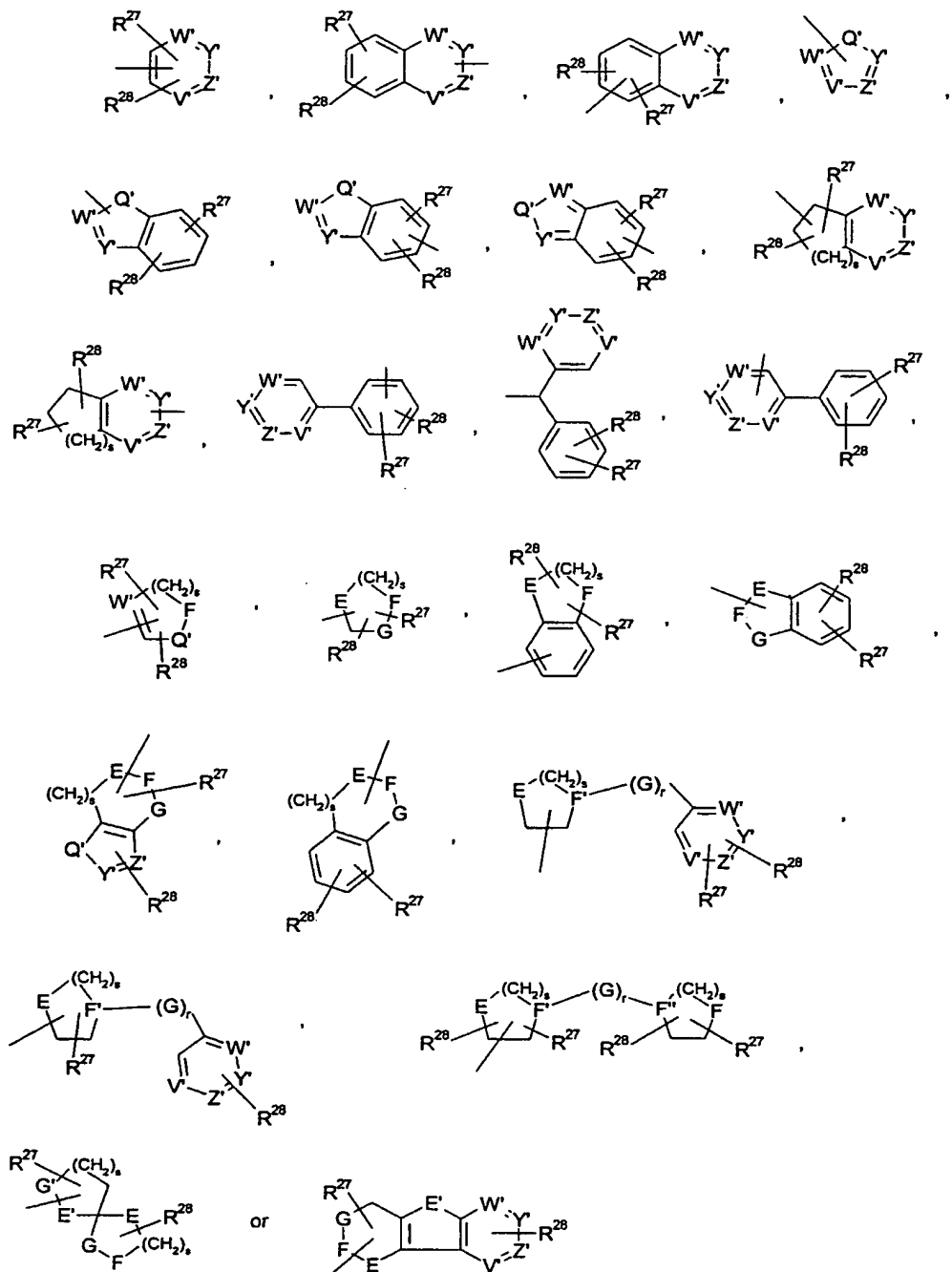
20

G'' is -OCH<sub>2</sub>CO-, -CH<sub>2</sub>CO-, -CO- or a valence bond; and

E'' is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH=CH-, -CH<sub>2</sub>NH- or -CH<sub>2</sub>CH<sub>2</sub>NH-;

25

D is hydrogen,



wherein:

5

r is 0 or 1;

s is 0, 1, 2 or 3;

E, E', F, G and G' independently are  $-\text{CHR}^{38}-$ ,  $>\text{C}=\text{O}$ ,  $>\text{NR}^{39}$ ,  $-\text{O}-$  or  $-\text{S}-$ ;

5 F' is  $>\text{CR}^{38}-$  or  $>\text{N}-$ ;

Y' is  $-\text{N}=\text{}$  or  $-\text{CR}^{32}=\text{}$ ;

Z' is  $-\text{N}=\text{}$  or  $-\text{CR}^{33}=\text{}$ ;

10

V' is  $-\text{N}=\text{}$  or  $-\text{CR}^{34}=\text{}$ ;

W' is  $-\text{N}=\text{}$  or  $-\text{CR}^{35}=\text{}$ ; and

15 Q' is  $-\text{NR}^{36}-$ ,  $-\text{O}-$  or  $-\text{S}-$ ;

wherein:

20  $\text{R}^{27}$ ,  $\text{R}^{28}$ ,  $\text{R}^{32}$ ,  $\text{R}^{33}$ ,  $\text{R}^{34}$  and  $\text{R}^{35}$  independently are hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{O}(\text{CH}_2)_y\text{CF}_3$ ,  $-(\text{CH}_2)_y\text{NHCOCF}_3$ ,  $-\text{NO}_2$ , lower alkyl, aryl, aryl-lower alkyl,  $-\text{SCF}_3$ ,  $-\text{SR}^{29}$ ,  $-\text{CHF}_2$ ,  $-\text{OCHF}_2$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{OSO}_2\text{R}^{29}$ ,  $-\text{OSO}_2\text{CF}_3$ ,  $-(\text{CH}_2)_y\text{CONR}^{29}\text{R}^{30}$ ,  $-\text{O}(\text{CH}_2)_y\text{CONR}^{29}\text{R}^{30}$ ,  $-(\text{CH}_2)_y\text{OR}^{29}$ ,  $-(\text{CH}_2)_y\text{NR}^{29}\text{R}^{30}$ ,  $-\text{OCOR}^{29}$ ,  $-\text{COR}^{29}$  or  $-\text{CO}_2\text{R}^{29}$ ;

or

25

$\text{R}^{27}$  and  $\text{R}^{28}$ ,  $\text{R}^{32}$  and  $\text{R}^{33}$ ,  $\text{R}^{33}$  and  $\text{R}^{34}$ , or  $\text{R}^{34}$  and  $\text{R}^{35}$  together form a bridge  $-\text{O}(\text{CH}_2)_y\text{O}-$ ;

wherein y is 0, 1, 2, 3 or 4; and

30  $\text{R}^{29}$  and  $\text{R}^{30}$  independently are hydrogen,  $-\text{COR}^{31}$ ,  $-\text{CO}_2\text{R}^{31}$ ,  $-\text{SO}_2\text{R}^{31}$ , lower alkyl, aryl or aryl-lower alkyl;

wherein  $\text{R}^{31}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

$R^{36}$  and  $R^{39}$  independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

$R^{38}$  is hydrogen,  $-OR^{40}$ ,  $-NR^{40}R^{41}$ , lower alkyl, aryl, aryl-lower alkyl,  $-SCF_3$ ,  $-SR^{40}$ ,  $-CHF_2$ ,  $-OCHF_2$ ,  $-OCF_2CHF_2$ ,  $-CONR^{40}R^{41}$ ,  $-(CH_2)_xCONR^{40}R^{41}$ ,  $-O(CH_2)_xCONR^{40}R^{41}$ ,  $-(CH_2)_xOR^{40}$ ,  
 5  $-(CH_2)_xNR^{40}R^{41}$ ,  $-OCOR^{40}$  or  $-CO_2R^{40}$ ;

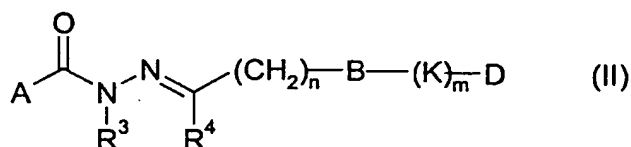
wherein x is 1, 2, 3 or 4;

$R^{40}$  and  $R^{41}$  independently are hydrogen,  $-COR^{42}$ ,  $-SO_2R^{42}$ , lower alkyl, aryl or aryl-lower al-  
 10 kyl;

wherein  $R^{42}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of  
 15 these or a pharmaceutically acceptable salt thereof.

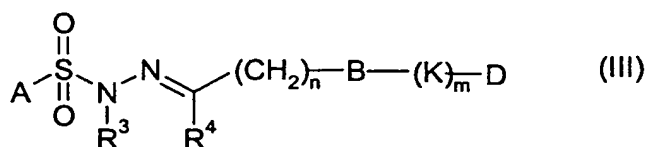
2. A compound according to claim 1 having the following formula II:



20

wherein A, B, K, D,  $R^3$ ,  $R^4$ , n and m are as defined in claim 1.

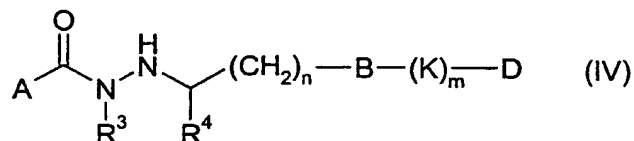
3. A compound according to claim 1 having the following formula III:



25

wherein A, B, K, D,  $R^3$ ,  $R^4$ , n and m are as defined in claim 1.

4. A compound according to claim 1 having the following formula IV:



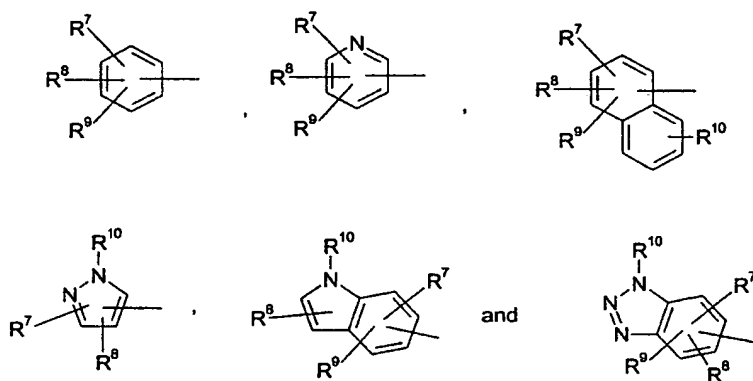
- 5 wherein A, B, K, D, R<sup>3</sup>, R<sup>4</sup>, n and m are as defined in claim 1.

5. A compound according to any one of the preceding claims, wherein R<sup>3</sup> is hydrogen.

6. A compound according to any one of the preceding claims, wherein R<sup>4</sup> is hydrogen.

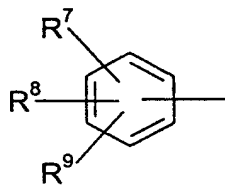
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7. A compound according to any one of the preceding claims, wherein A is selected from the group consisting of



- 15 wherein R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined in claim 1.

8. A compound according to claim 7, wherein A is



20

wherein  $R^7$ ,  $R^8$  and  $R^9$  are as defined in claim 1.

9. A compound according to claim 7 or 8, wherein  $R^7$  is halogen, lower alkyl, -OH, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, -O-lower alkyl, aryl, aryl-lower alkyl, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -OCH<sub>2</sub>CONH<sub>2</sub>,  
 5 -NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -OCHF<sub>2</sub>, -CF<sub>3</sub> or -OCF<sub>3</sub>.

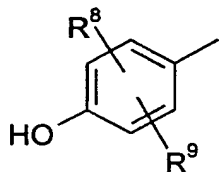
10. A compound according to any one of the claims 7 to 9, wherein  $R^8$  and  $R^9$  independently are hydrogen, halogen, -OH, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -OCF<sub>3</sub>, -SCF<sub>3</sub>, -CF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -O-lower alkyl, lower alkyl or phenyl and  $R^{10}$  is hydrogen, lower alkyl or phenyl.

10

11. A compound according to claim 10, wherein  $R^8$  and  $R^9$  independently are hydrogen, halogen, -O-lower alkyl, -NH<sub>2</sub>, -CN or -NO<sub>2</sub> and  $R^{10}$  is hydrogen.

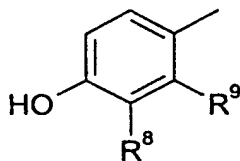
12. A compound according to claim 8, wherein A is

15



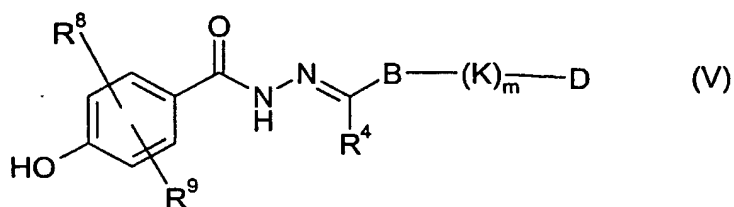
wherein  $R^8$  and  $R^9$  independently are as defined in any one of the claims 10 or 11.

- 20 13. A compound according to claim 12, wherein A is



wherein  $R^8$  is hydrogen, halogen, -O-lower alkyl, -NH<sub>2</sub>, -CN or -NO<sub>2</sub>; and  $R^9$  is hydrogen or  
 25 halogen.

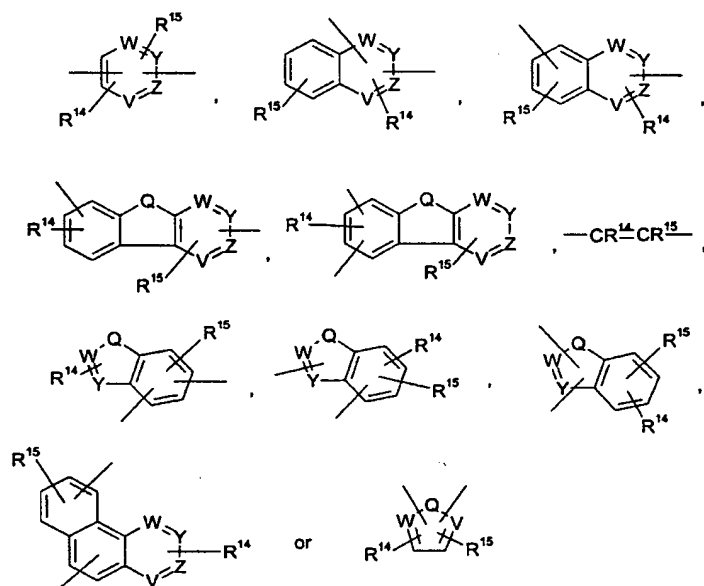
14. A compound according to any one of the claims 7 to 13 having the following formula  
 V:



wherein R<sup>8</sup> and R<sup>9</sup> are as defined in any one of the claims 1, 10, 11 or 13 and R<sup>4</sup>, B, K, D and m are as defined in claim 1.

5

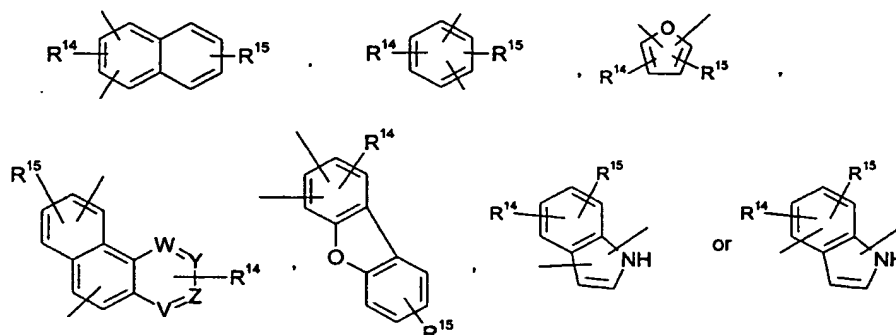
15. A compound according to any one of the preceding claims, wherein B is



wherein V, W, Z, Y and Q are as defined in claim 1; and R<sup>14</sup> and R<sup>15</sup> independently are hydro-  
gen, halogen, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OR<sup>16</sup>, -NR<sup>16</sup>R<sup>17</sup>, lower alkyl, aryl, aryl-lower alkyl, -OSO<sub>2</sub>CF<sub>3</sub>,  
10 -CONR<sup>16</sup>R<sup>17</sup>, -CH<sub>2</sub>OR<sup>16</sup>, -CH<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>, -OCOR<sup>16</sup> or -CO<sub>2</sub>R<sup>18</sup>, or R<sup>14</sup> and R<sup>15</sup> together form a  
bridge -OCH<sub>2</sub>O- or -(CH<sub>2</sub>)<sub>n</sub>-; wherein I, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> are as defined in claim 1.

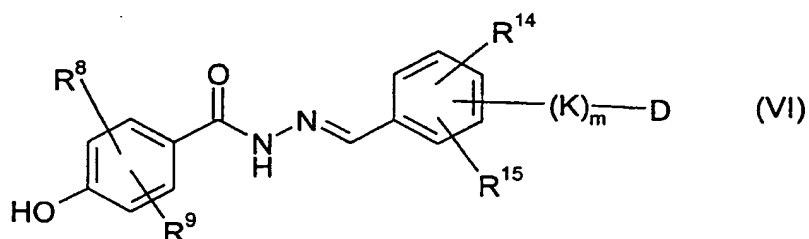
16. A compound according to claim 15, wherein Q is -O- or -NH-.

17. A compound according to claim 15, wherein B is



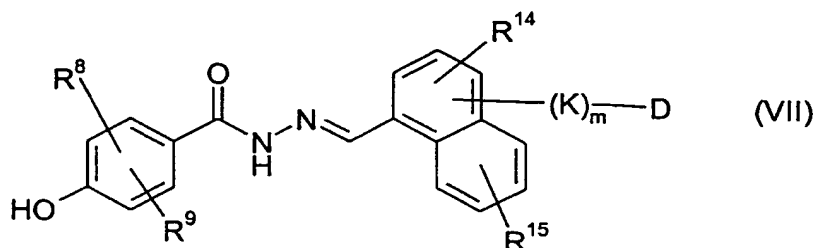
wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15, and V, W, Z and Y are as defined in claim 1.

18. A compound according to claim 17 having the following formula VI:



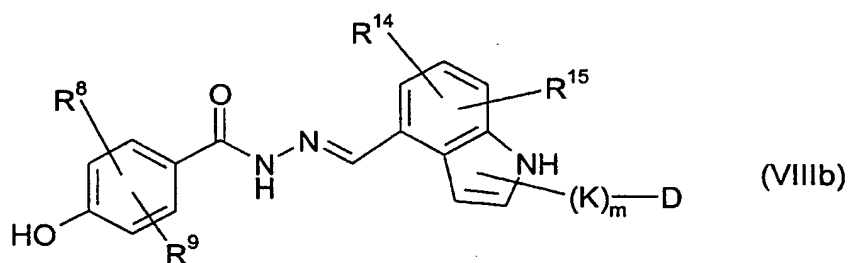
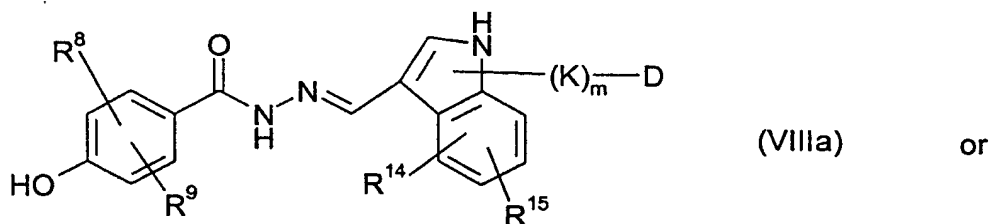
wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  and  $R^9$  are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

19. A compound according to claim 17 having the following formula VII:



wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  and  $R^9$  are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

20. A compound according to claim 17 having the following formulae VIIIa or VIIIb:

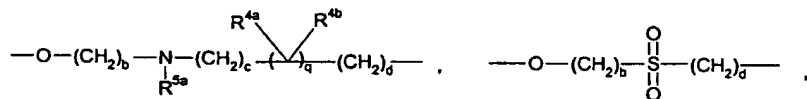
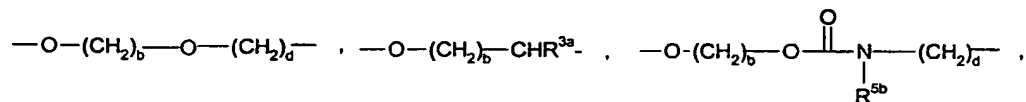
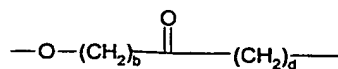
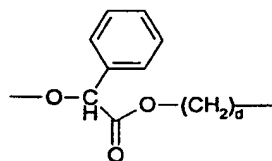
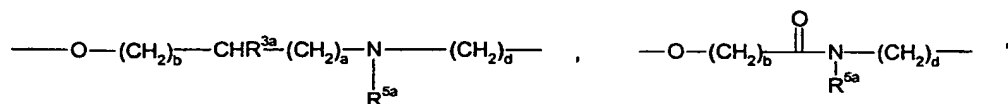
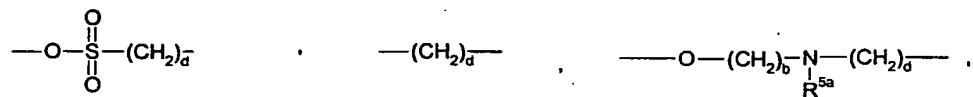
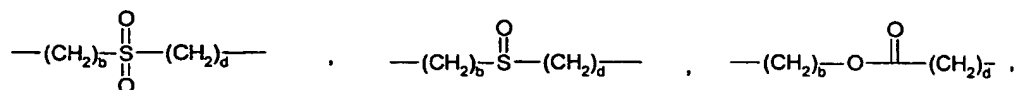
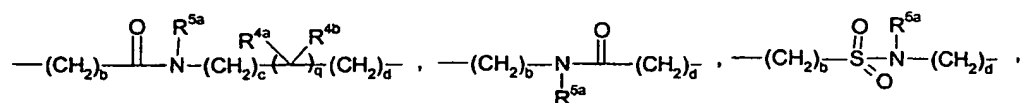
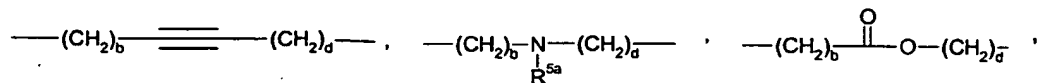
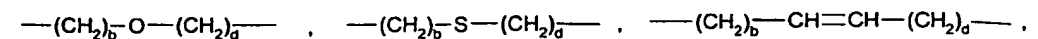


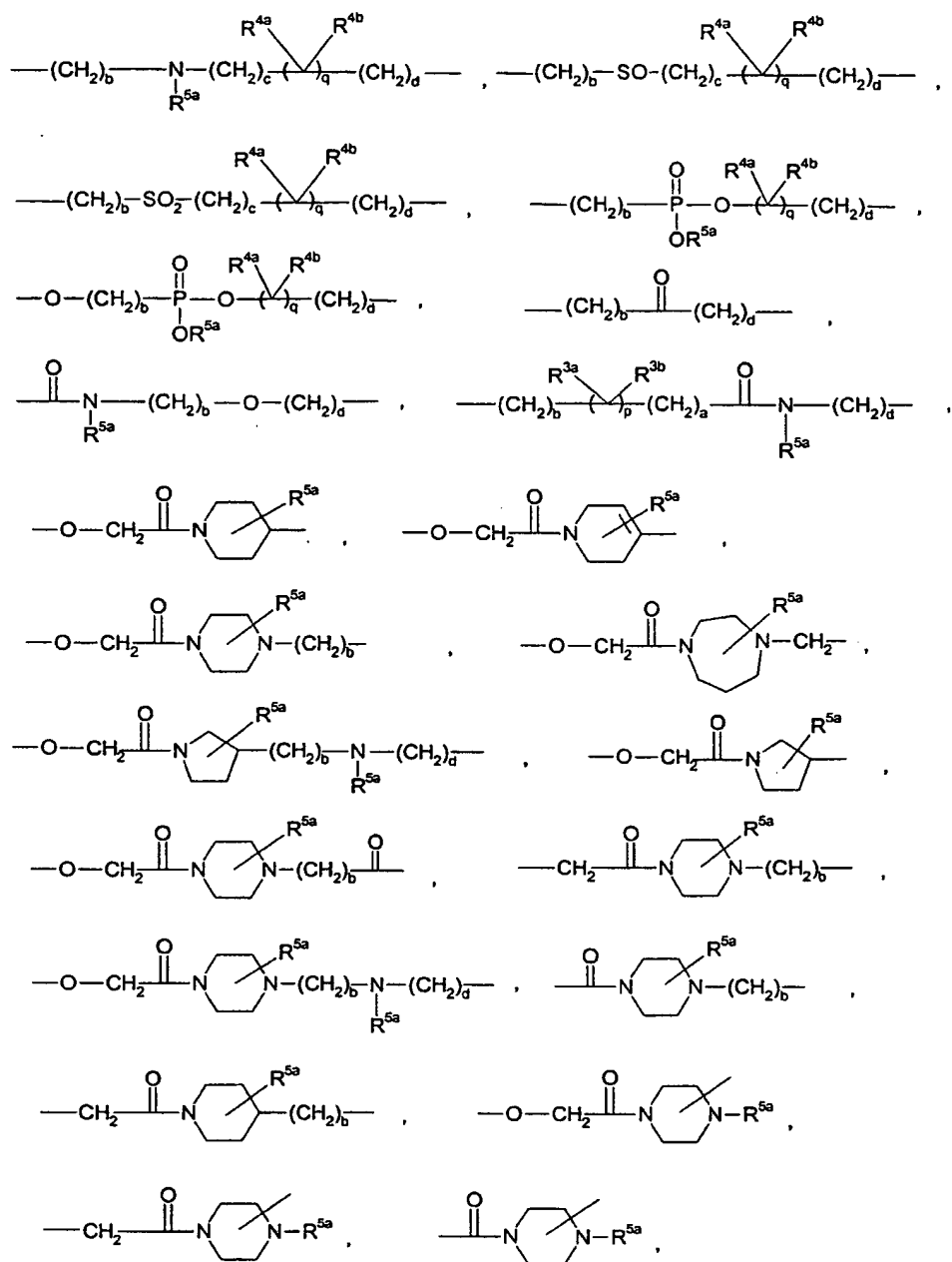
5 wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  and  $R^9$  are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

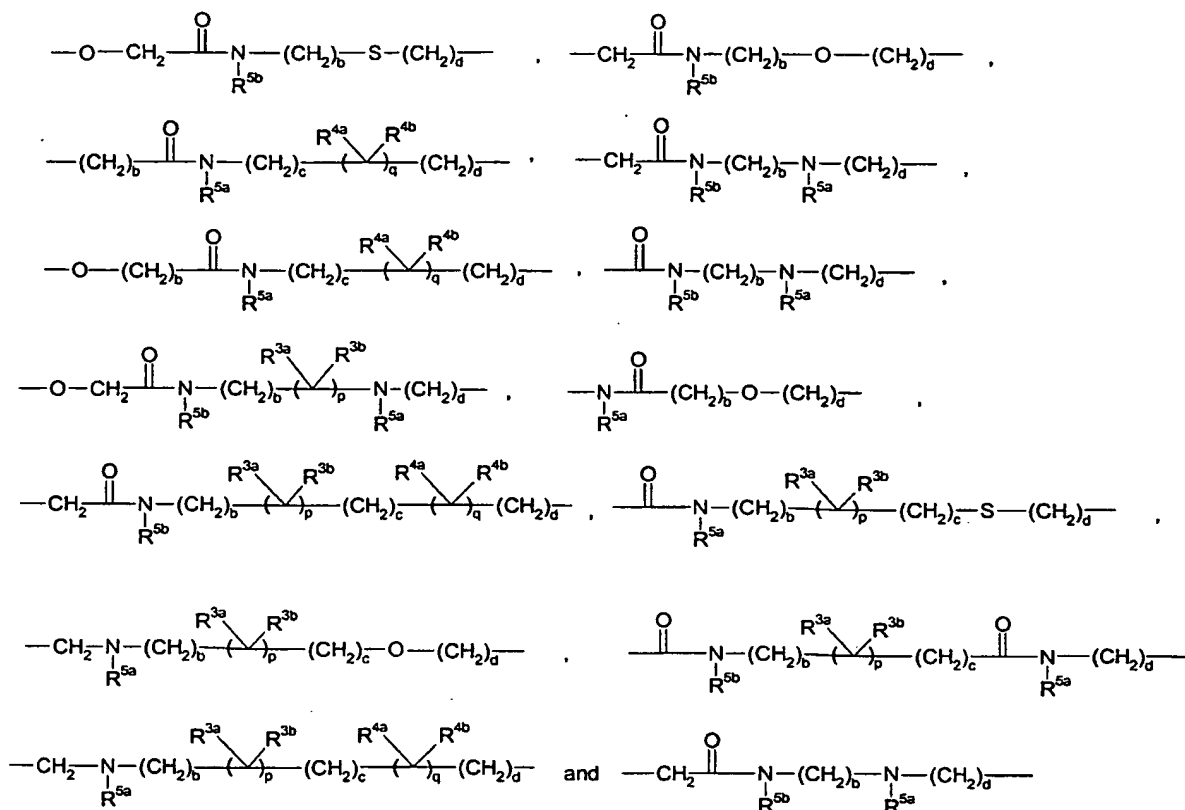
21. A compound according to any one of the claims 15 to 20, wherein  $R^{14}$  and  $R^{15}$  independently are hydrogen, halogen, lower alkyl, -O-lower alkyl or aryl.

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22. A compound according to any one of the preceding claims, wherein K is selected from the group consisting of

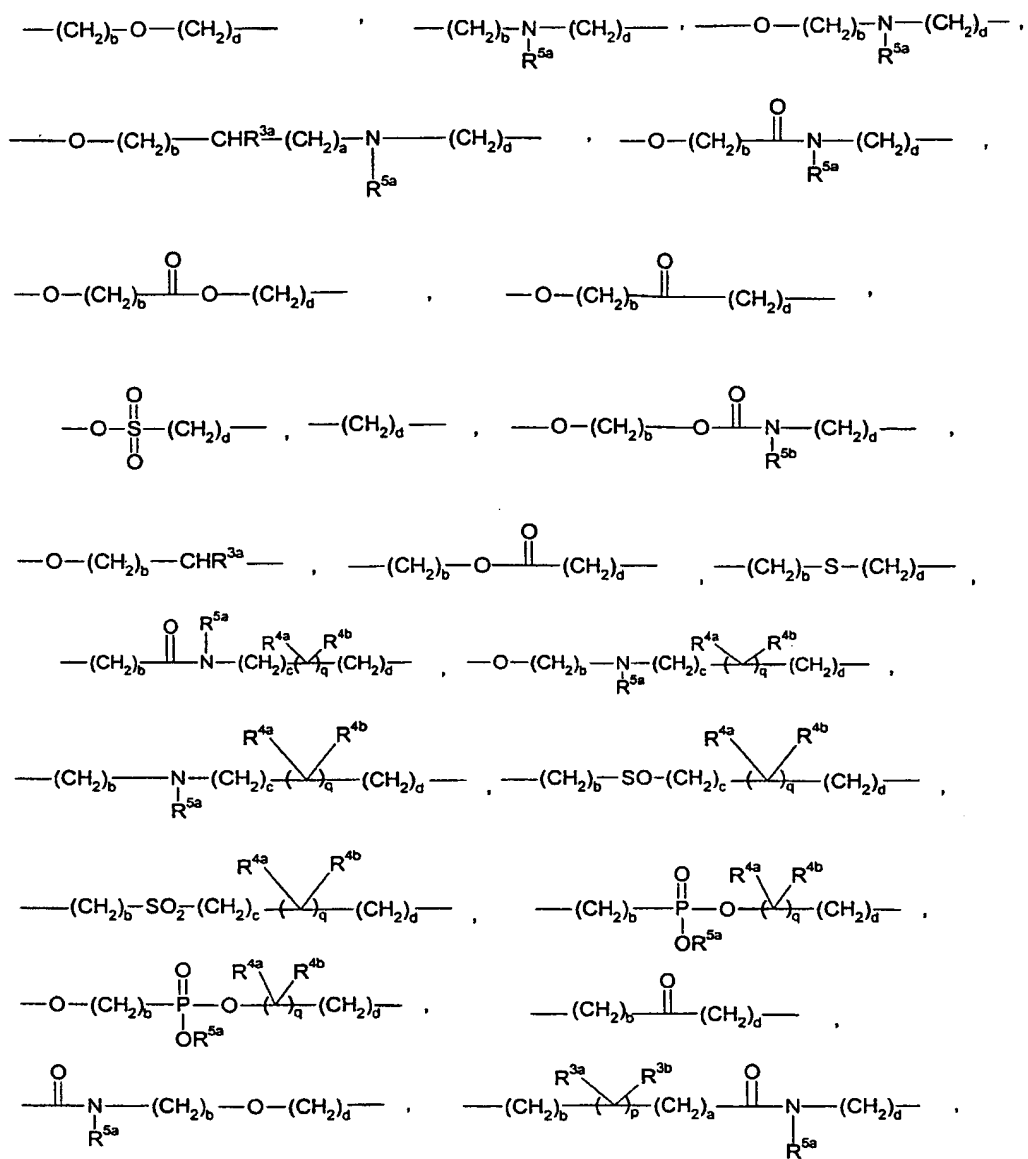




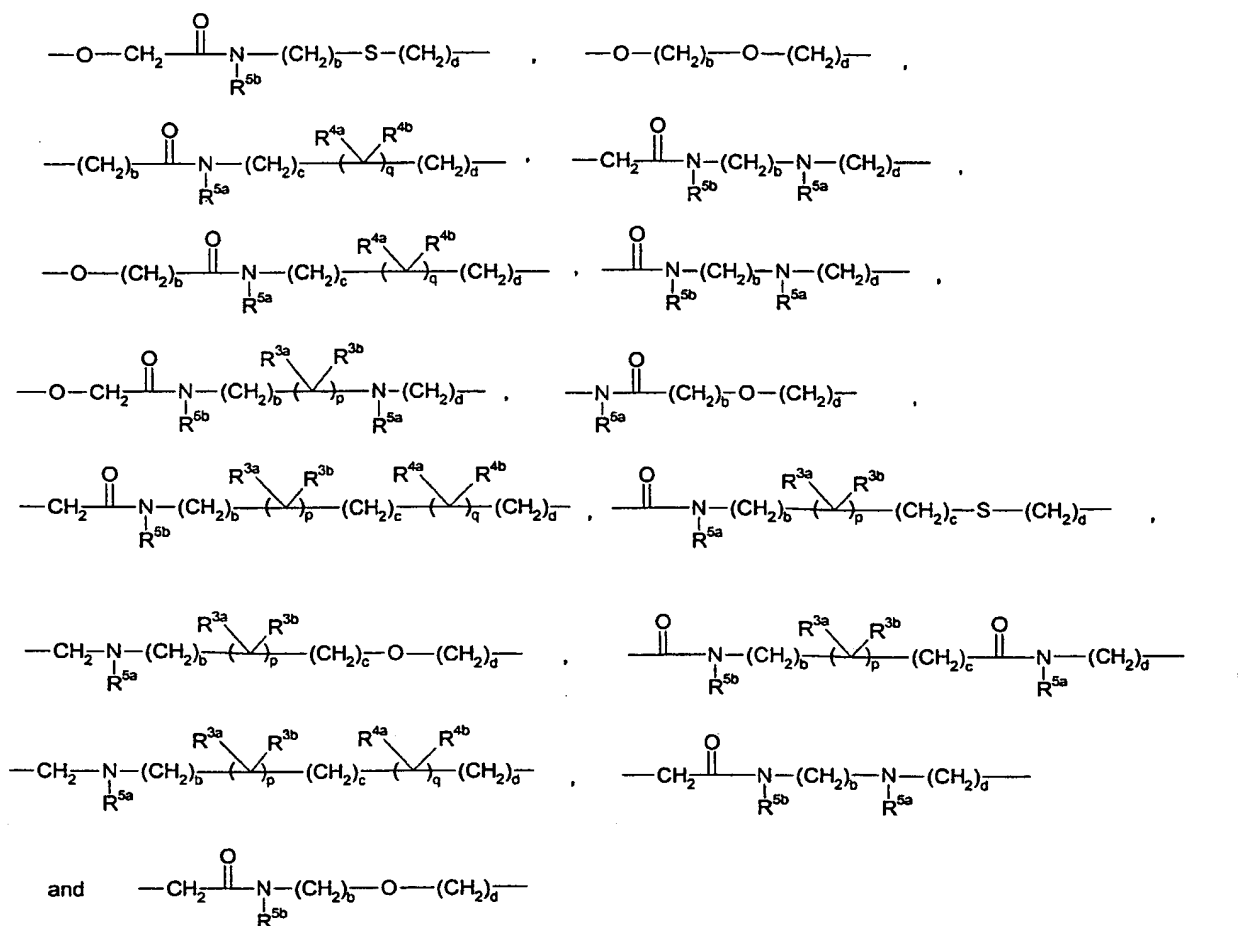


wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined in claim 1.

- 5 23. A compound according to claim 22, wherein K is selected from the group consisting of

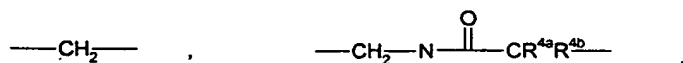
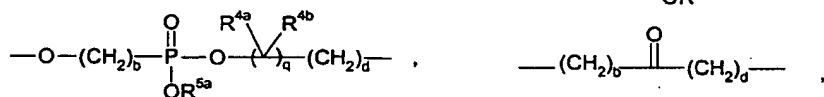
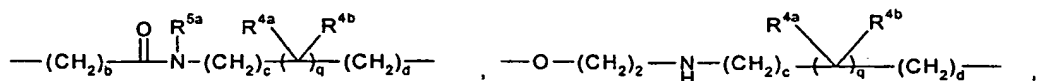
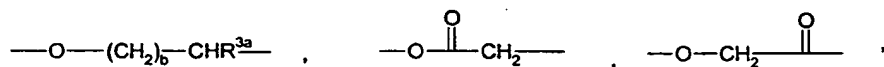
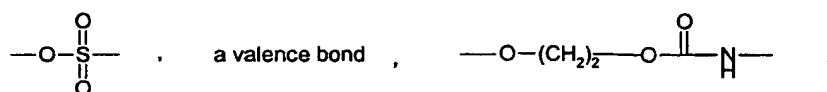
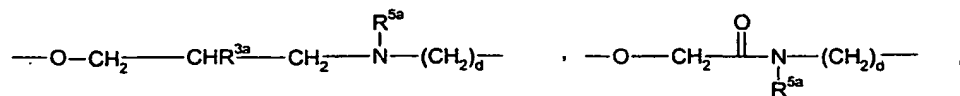
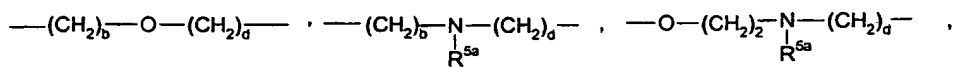




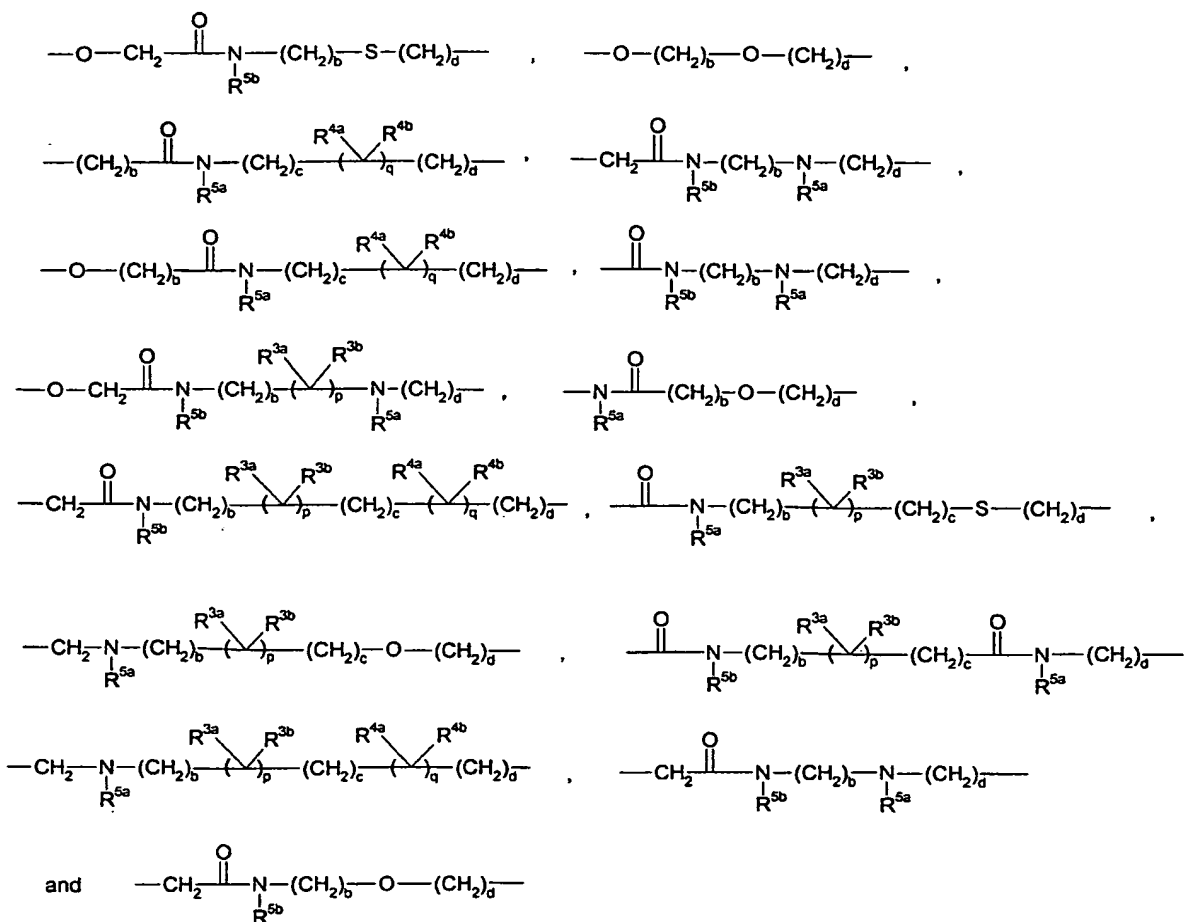


wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined in claim 1.

- 5 24. A compound according to claim 23, wherein K is selected from the group consisting of







wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined in claim 1.

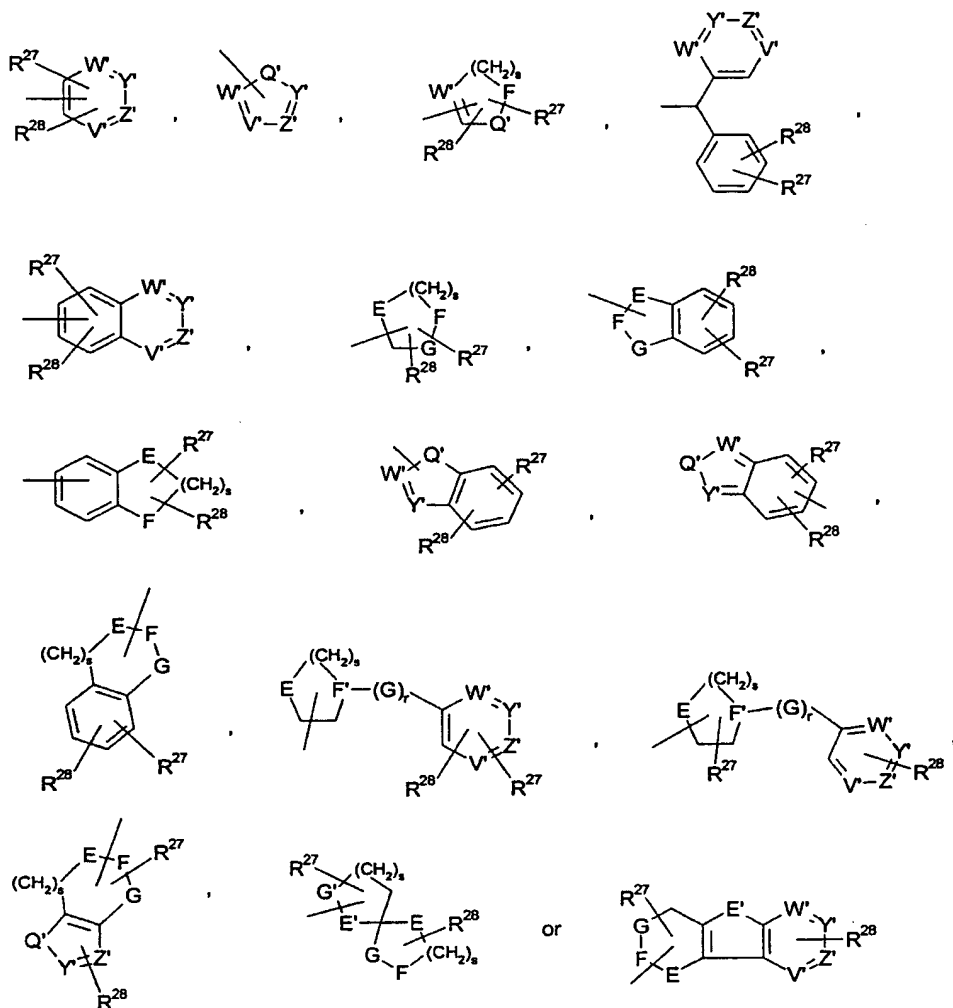
- 5 25. A compound according to any one of the claims 22 to 24, wherein  $R^{5a}$  and  $R^{5b}$  independently are hydrogen, lower alkyl,  $-\text{OH}$ ,  $-(\text{CH}_2)_k\text{OR}^{6a}$ , aryl, aryl-lower alkyl,  $-\text{CH}_2\text{CF}_3$ ,  $-(\text{CH}_2)_g\text{-COOR}^{43}$ ,  $-\text{COOR}^{43}$ ,  $-(\text{CH}_2)_k\text{-CN}$  or  $-(\text{CH}_2)_k\text{-NR}^{6a}\text{R}^{6b}$  wherein  $g$ ,  $k$ ,  $R^{43}$ ,  $R^{6a}$  and  $R^{6b}$  are as defined in claim 1.

- 10 26. A compound according to claim 25, wherein  $g$  and  $k$  independently are 1, 2 or 3,  $R^{6a}$  and  $R^{6b}$  independently are hydrogen, lower alkyl such as methyl or ethyl, or aryl such as phenyl,

27. A compound according to any one of the claims 22 to 26, wherein  $R^{3a}$  and  $R^{3b}$  independently are hydrogen, halogen, -OH, -O-lower alkyl, -COO-lower alkyl, lower alkyl or aryl-lower alkyl.

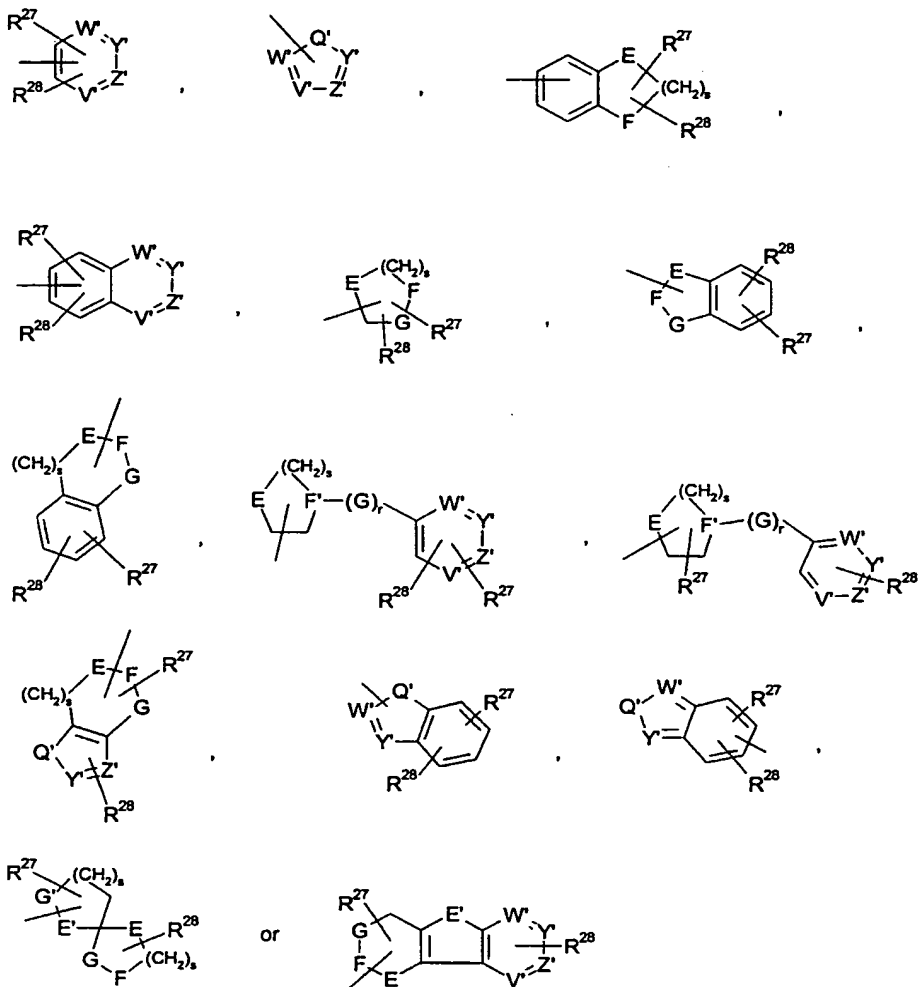
5 28. A compound according to any one of the claims 22 to 27, wherein  $R^{4a}$  and  $R^{4b}$  independently are hydrogen, -CN, -CONH<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -O-lower alkyl, -CH<sub>2</sub>OH, -CH<sub>2</sub>O-aryl, -N(CH<sub>3</sub>)<sub>2</sub>, -OH, -CO<sub>2</sub>-lower alkyl or lower alkyl.

29. A compound according to any one of the preceding claims, wherein D is hydrogen,



wherein  $s$ ,  $r$ ,  $R^{27}$ ,  $R^{28}$ ,  $V'$ ,  $Y'$ ,  $Q'$ ,  $Z'$ ,  $W'$ ,  $E$ ,  $E'$ ,  $F$ ,  $F'$ ,  $G$  and  $G'$  are as defined in claim 1.

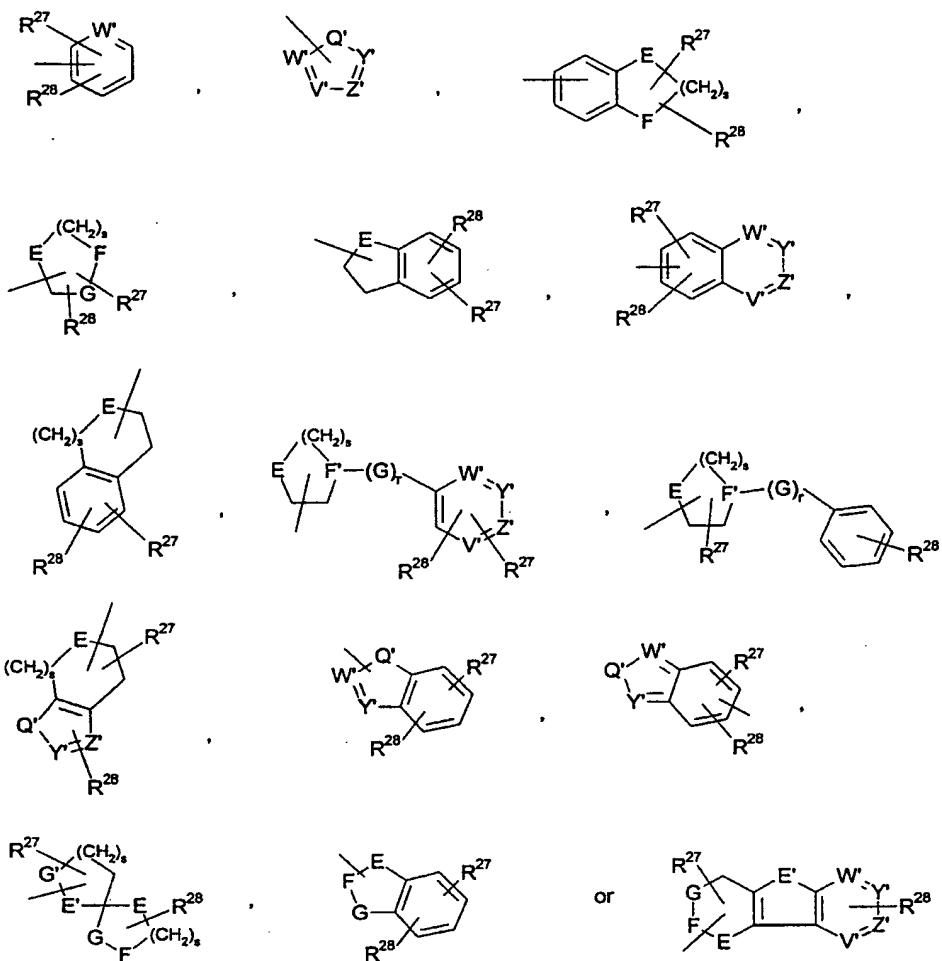
30. A compound according to claim 29, wherein D is hydrogen,



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wherein s, r,  $R^{27}$ ,  $R^{28}$ ,  $V'$ ,  $Y'$ ,  $Z'$ ,  $Q'$ ,  $Z'$ ,  $W'$ ,  $E$ ,  $E'$ ,  $F$ ,  $F'$ ,  $G$  and  $G'$  are as defined in claim 1.

31. A compound according to claim 29, wherein D is hydrogen,



wherein E and E' independently are  $>\text{CHR}^{38}$ ,  $>\text{NR}^{39}$  or  $-\text{O}-$ ; F, G and G' independently are  
 5  $>\text{CHR}^{38}$ ,  $>\text{C}=\text{O}$  or  $>\text{NR}^{39}$ ; F' is  $>\text{CR}^{38}-$  or  $>\text{N}-$ ; and s, r,  $\text{R}^{27}$ ,  $\text{R}^{28}$ ,  $\text{R}^{38}$ ,  $\text{R}^{39}$ ,  $\text{V}'$ ,  $\text{Y}'$ ,  $\text{Z}'$ ,  $\text{Q}'$  and  $\text{W}'$   
 are as defined in claim 1.

32. A compound according to any one of the claims 29 to 31, wherein  $\text{R}^{27}$  and  $\text{R}^{28}$  inde-  
 10  $-(\text{CH}_2)_y\text{NHCOCF}_3$ ;  $-\text{NHCOCF}_3$ ;  $-\text{CN}$ ;  $-\text{NO}_2$ ;  $-\text{COR}^{29}$ ,  $-\text{COOR}^{29}$ ,  $-(\text{CH}_2)_y\text{OR}^{29}$  or  $-\text{OR}^{29}$  wherein  
 $\text{R}^{29}$  is hydrogen, aryl or lower alkyl and y is 1, 2, 3 or 4; lower alkyl such as methyl, ethyl,  
 2-propenyl, isopropyl, tert-butyl or cyclohexyl; lower alkylthio;  $-\text{SCF}_3$ ; aryl such as phenyl;  
 $-(\text{CH}_2)_y\text{NR}^{29}\text{R}^{30}$  or  $-\text{NR}^{29}\text{R}^{30}$  wherein  $\text{R}^{29}$  and  $\text{R}^{30}$  independently are hydrogen,  $-\text{COO}-$ lower  
 15  $-\text{OCH}_2\text{O}-$ ;  $\text{R}^{38}$  is hydrogen;  $-\text{OCHF}_2$ ;  $-\text{OR}^{40}$  wherein  $\text{R}^{40}$  is hydrogen or lower alkyl; lower alkyl

such as methyl, isopropyl or tert-butyl; lower alkylthio; -SCF<sub>3</sub>; -CH<sub>2</sub>OH; -COO-lower alkyl or -CONH<sub>2</sub>; and R<sup>39</sup> is hydrogen, lower alkyl, aryl or aryl-lower alkyl.

33. A compound according to any one of the claims 1 to 32 for use as a medicament.

5

34. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 32 together with one or more pharmaceutically acceptable carriers or excipients.

10 35. A pharmaceutical composition according to claim 34 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 1 to 32.

15 36. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 32.

20 37. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 32.

38. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 1 to 32.

25 39. The method according to any one of the claims 36 to 38 comprising administering to a subject in need thereof an amount of the compound as defined in claim 1 to 33 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

30

40. Use of a compound according to any one of the claims 1 to 32 for the manufacture of a medicament for treating type I or type II diabetes.

41. Use of a compound according to any one of the claims 1 to 32 for the manufacture of a medicament for treating hyperglycemia.

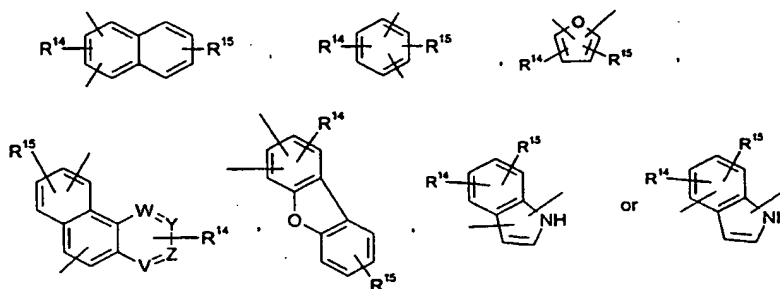
42. Use of a compound according to any one of the claims 1 to 32 for the manufacture  
5 of a medicament for lowering blood glucose in a mammal.

43. A compound according to any one of the claims 1 to 32 characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay I or Glucagon Binding Assay II disclosed herein corresponding to an  $IC_{50}$  value of less than 1  $\mu$ M, preferably of less than 500 nM and even more preferred of less than 100 nM.  
10

## AMENDED CLAIMS

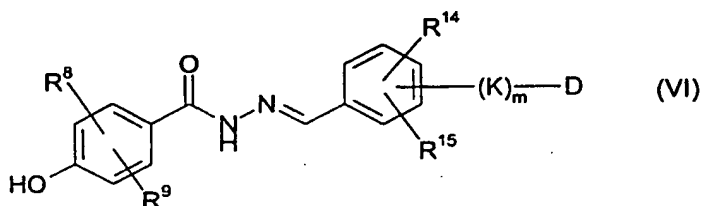
[received by the International Bureau on 01 December 1998 (01.12.98);  
original claims 19-43 replaced by new claims 19-47;  
remaining claims unchanged (18 pages)]

17. A compound according to claim 15, wherein B is



- 5 wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15, and V, W, Z and Y are as defined in claim 1.

18. A compound according to claim 17 having the following formula VI:

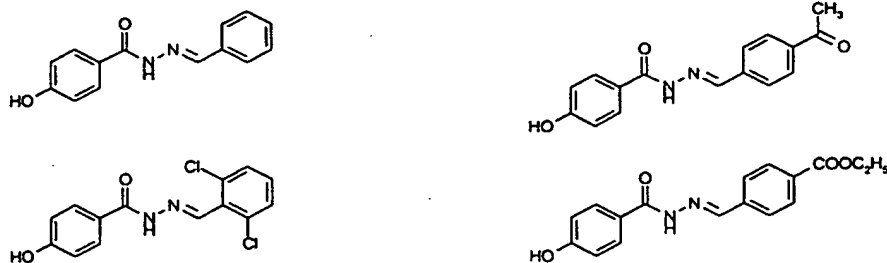


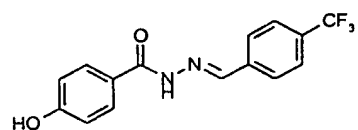
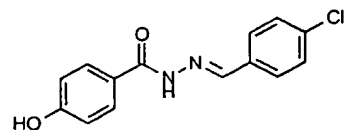
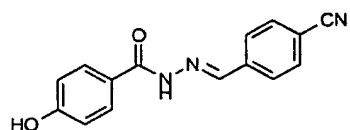
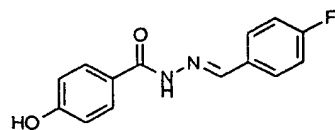
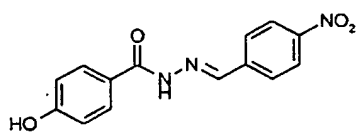
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- wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  and  $R^9$  are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

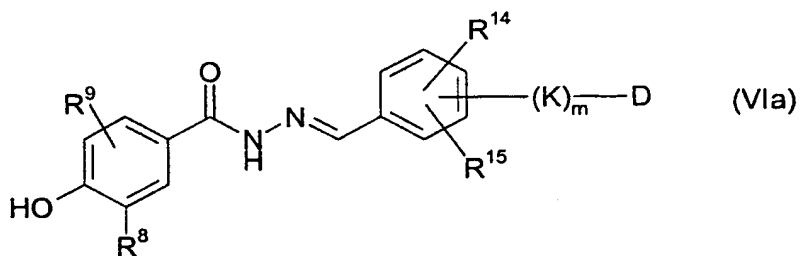
19. A compound according to claim 18 except for the following compounds:

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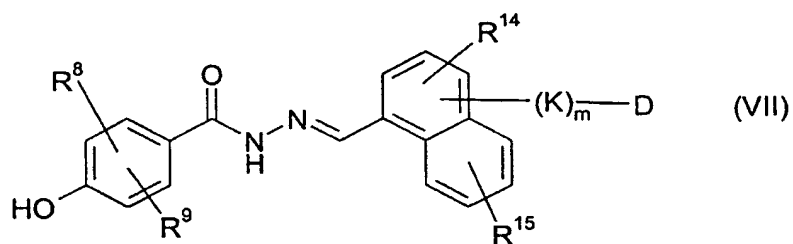
20. A compound according to claim 18 of the formula VIa:



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wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  is halogen,  $R^9$  is as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

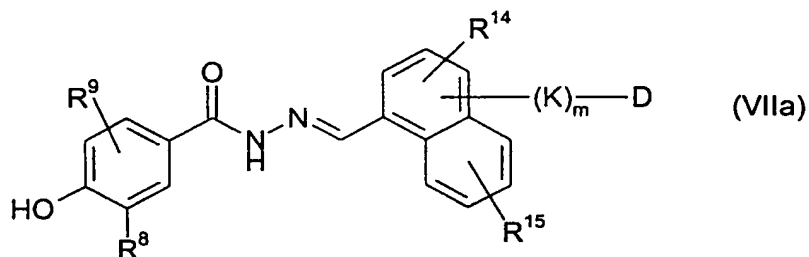
21. A compound according to claim 17 having the following formula VII:



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wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  and  $R^9$  are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

22. A compound according to claim 21 of the formula VIIa:

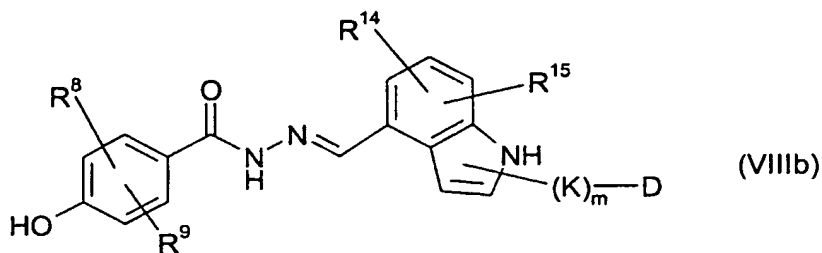
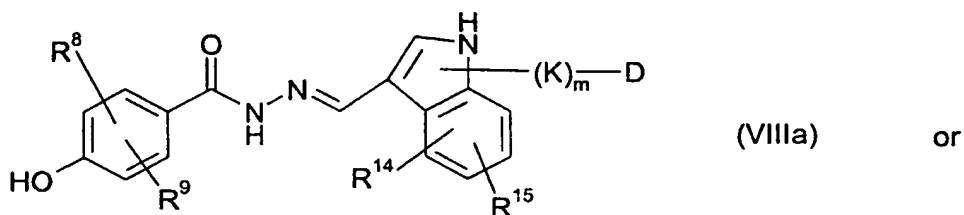


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wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  is halogen,  $R^9$  is as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

23. A compound according to claim 17 having the following formulae VIIIa or VIIIb:

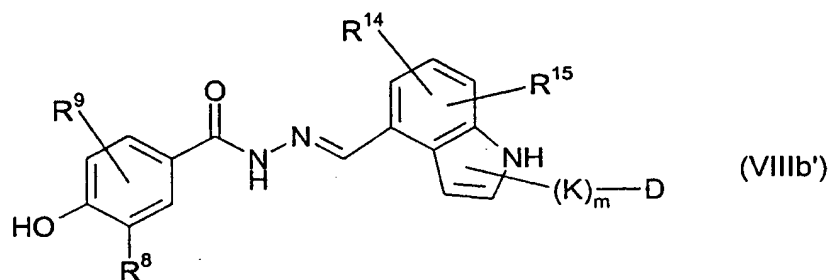
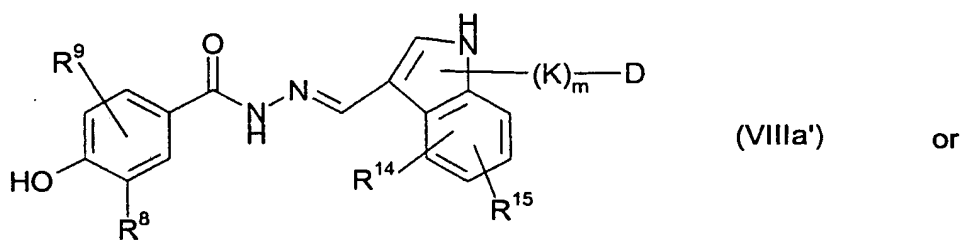
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wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  and  $R^9$  are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

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24. A compound according to claim 17 having the following formulae VIIIa' or VIIIb':



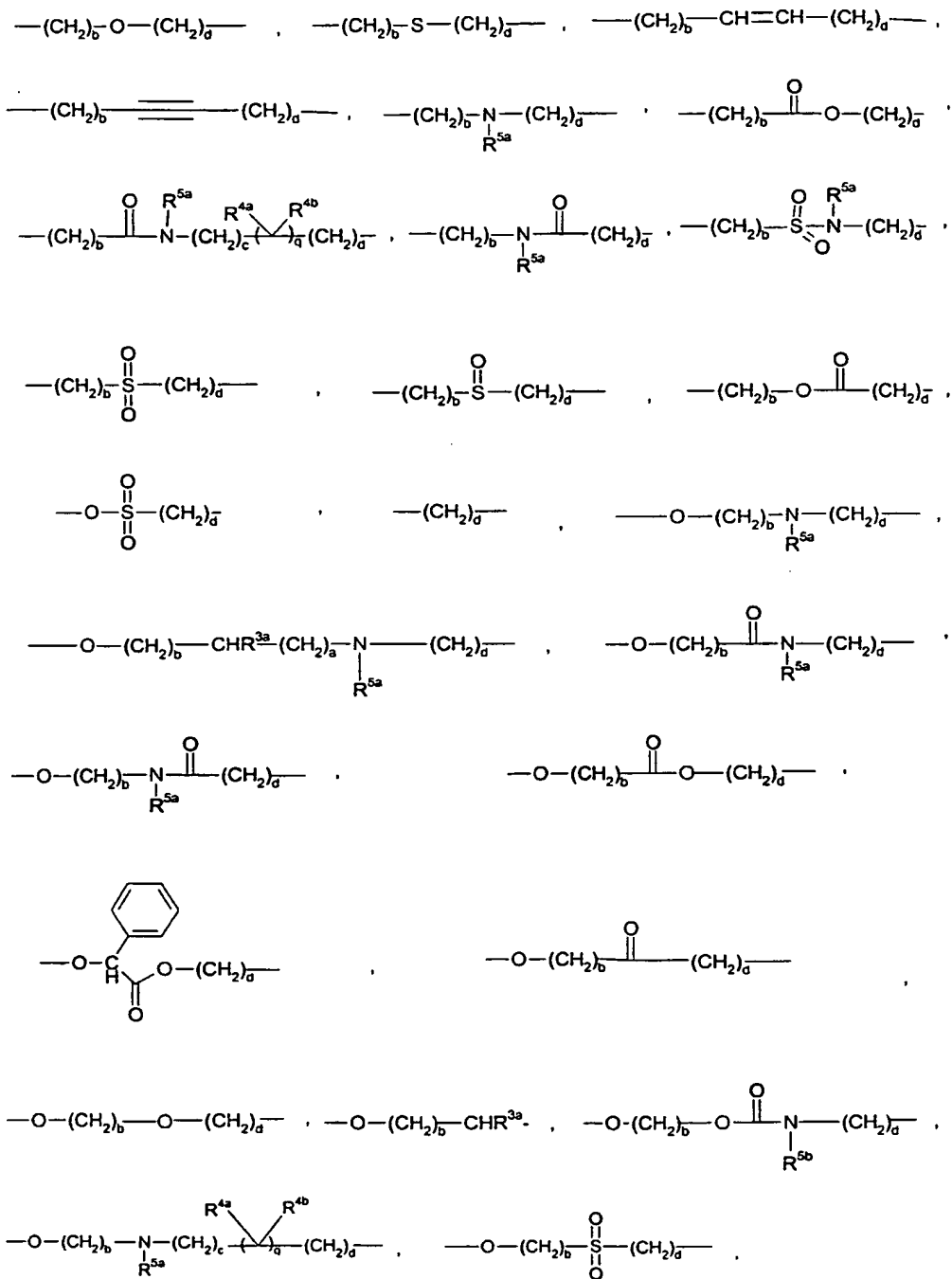
wherein  $R^{14}$  and  $R^{15}$  are as defined in claim 15,  $R^8$  is halogen,  $R^9$  is as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

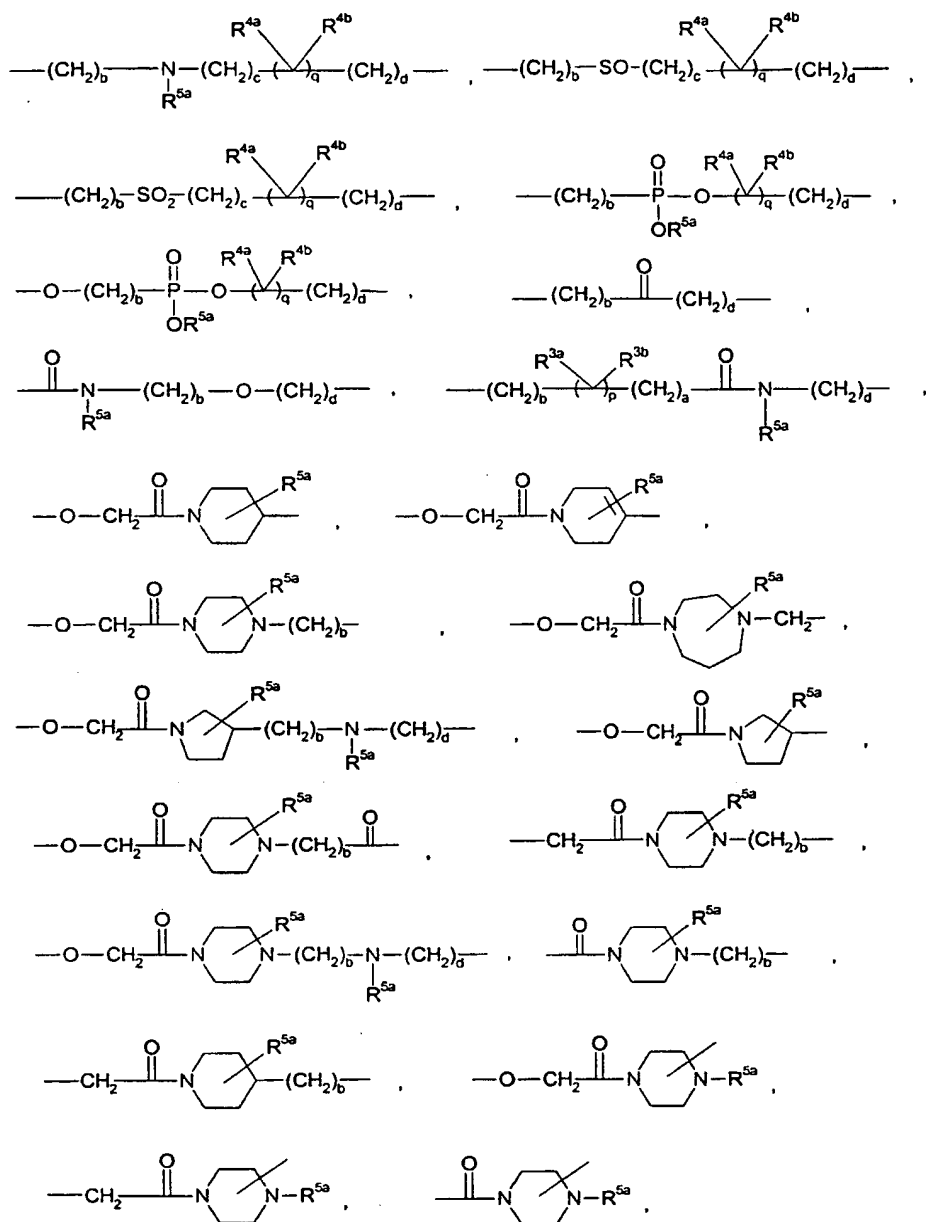
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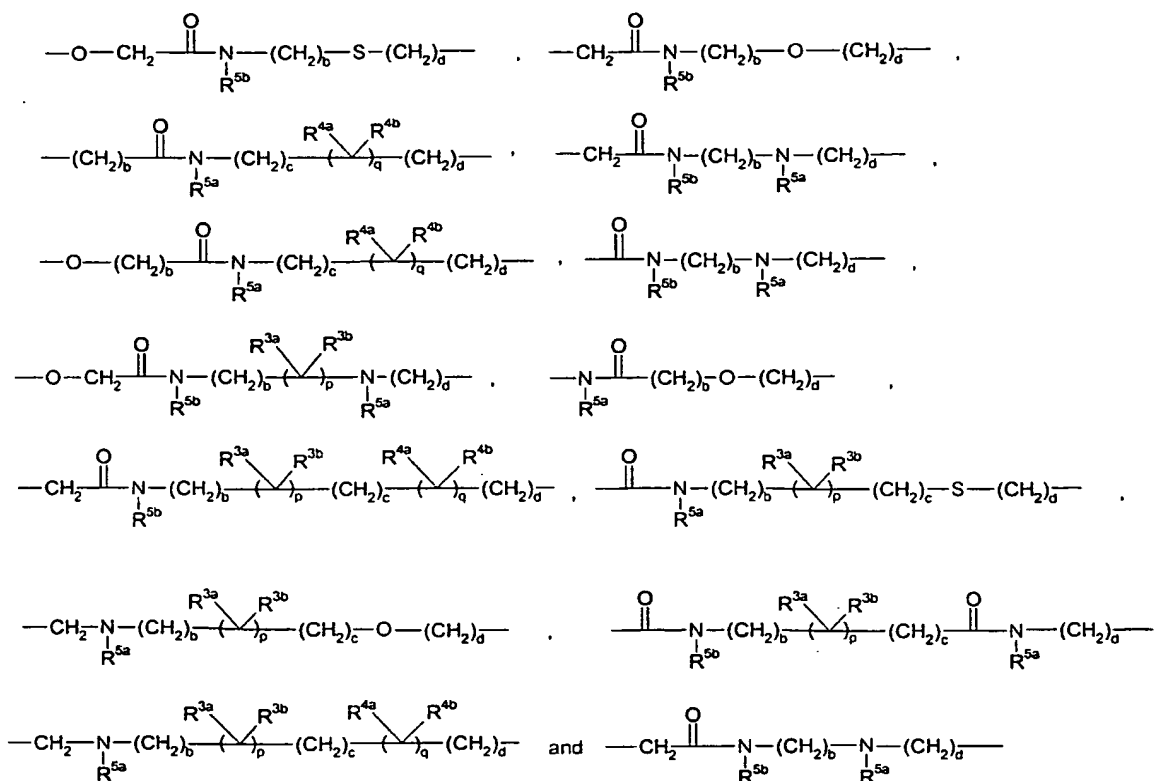
25. A compound according to any one of the claims 15 to 24, wherein  $R^{14}$  and  $R^{15}$  independently are hydrogen, halogen, lower alkyl, -O-lower alkyl or aryl.

26. A compound according to any one of the preceding claims, wherein K is selected from the group consisting of

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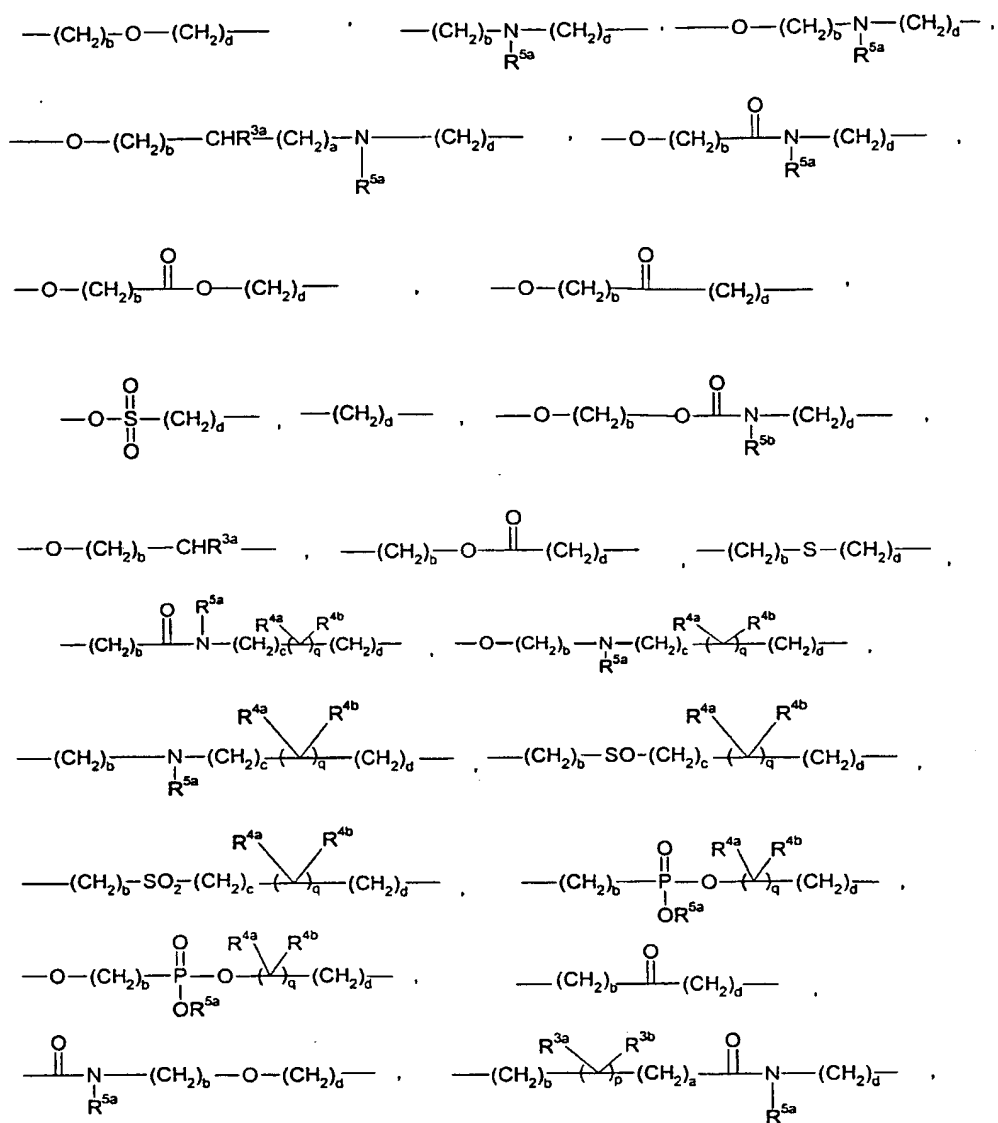


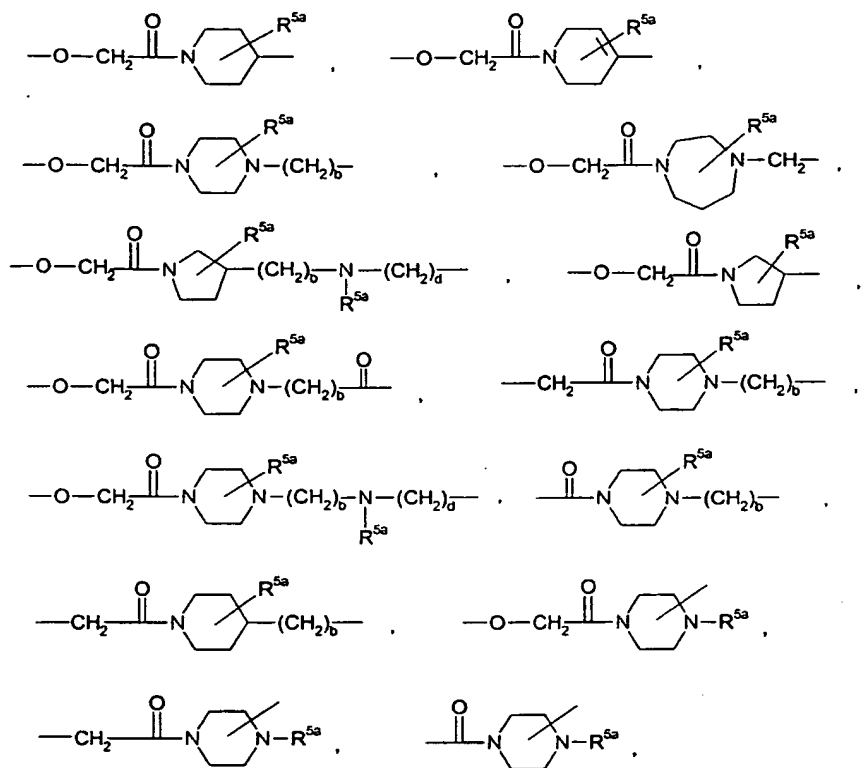


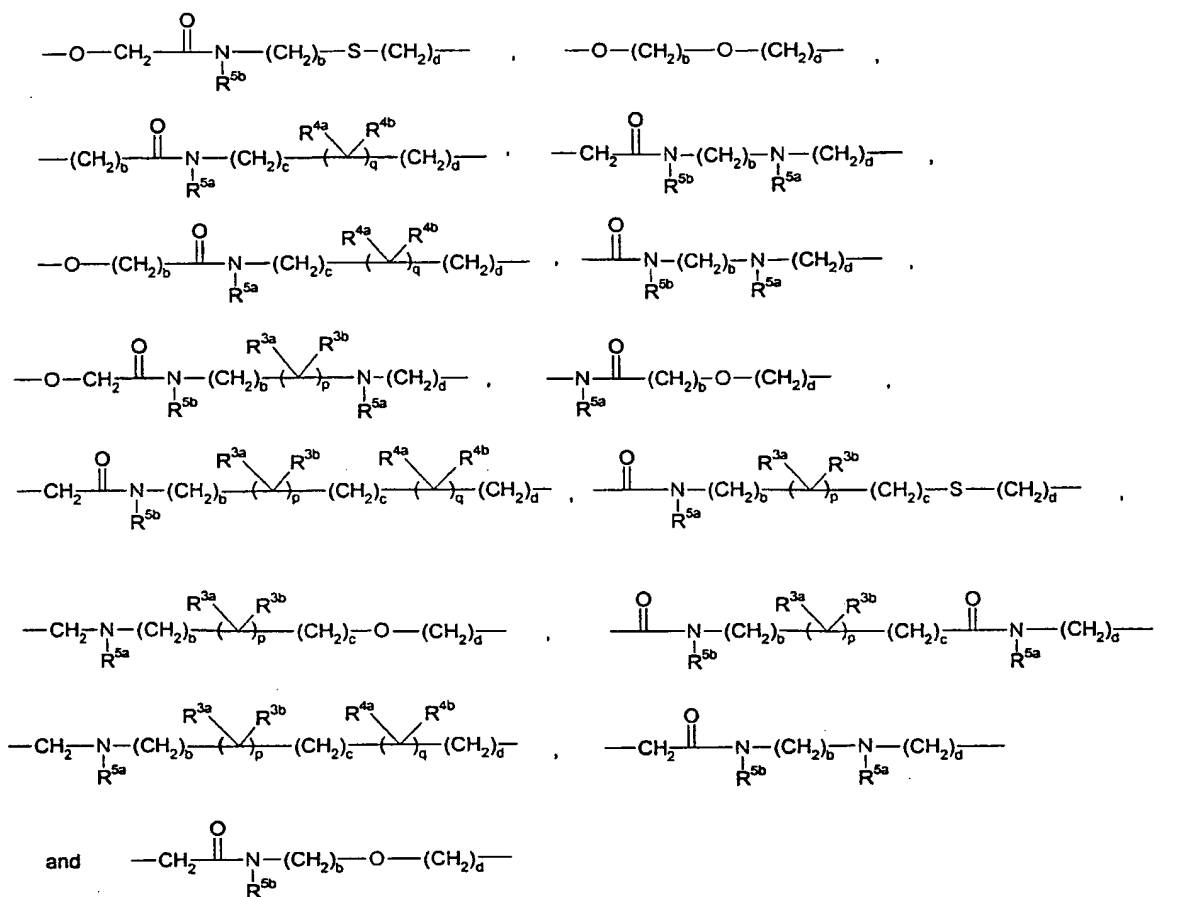


wherein R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup>, R<sup>5a</sup>, R<sup>5b</sup>, a, b, c, d, p and q are as defined in claim 1.

- 5     27.     A compound according to claim 26, wherein K is selected from the group consisting  
of

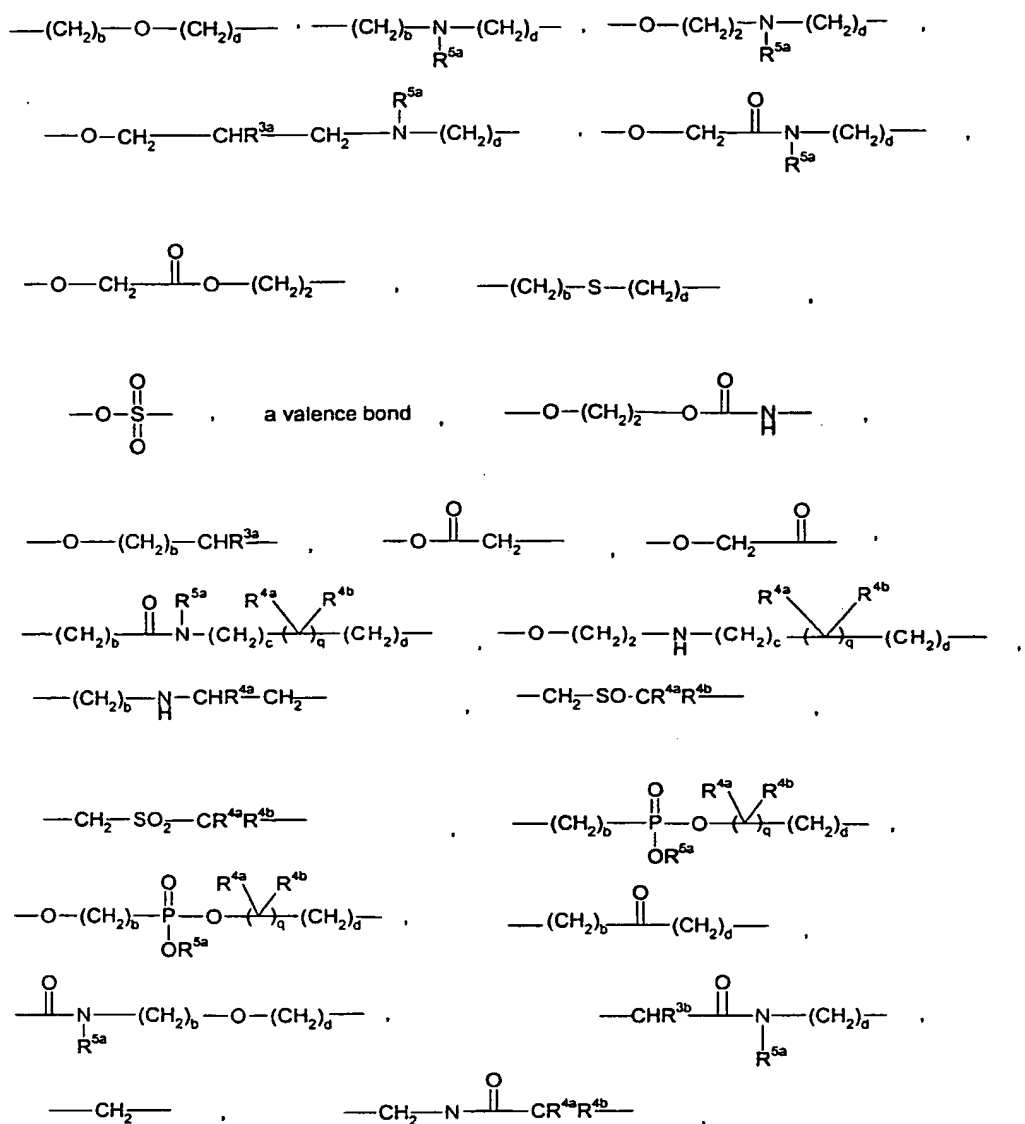




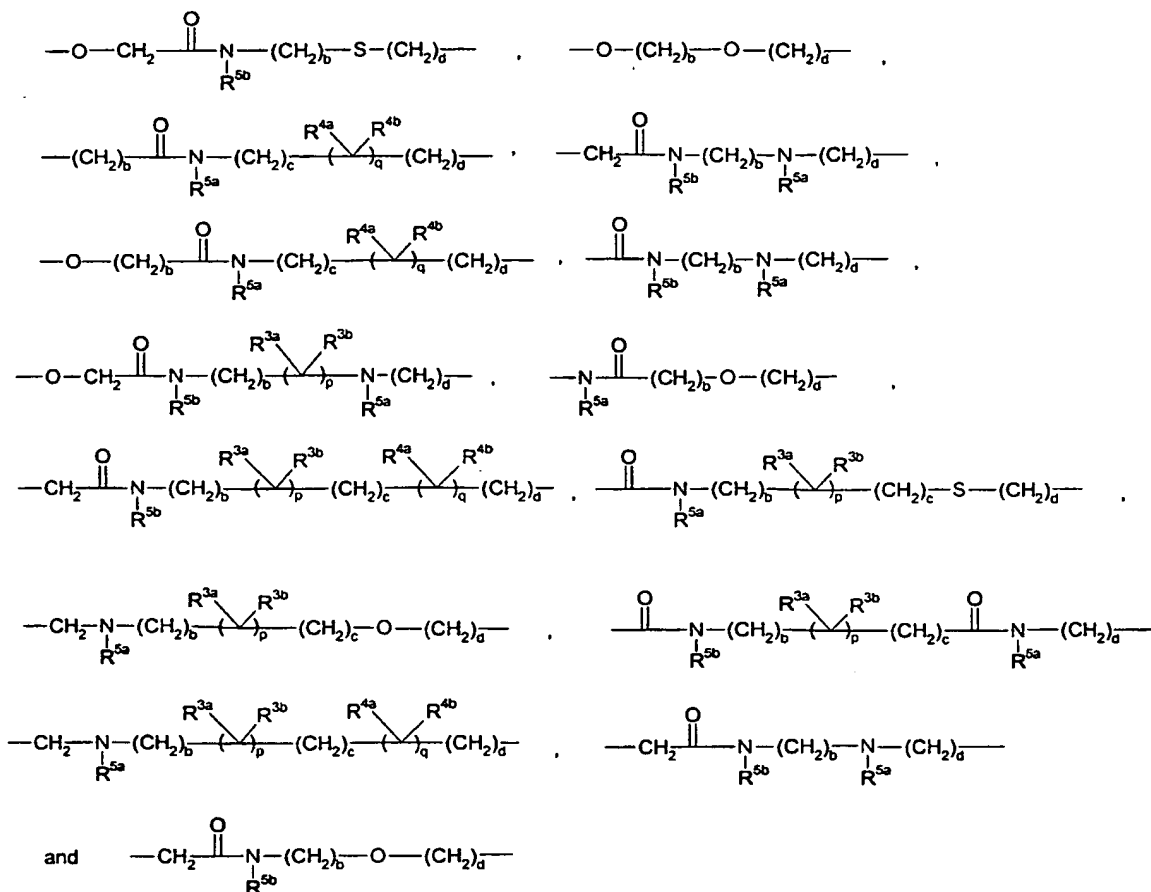


wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined in claim 1.

- 5 28. A compound according to claim 27, wherein K is selected from the group consisting of







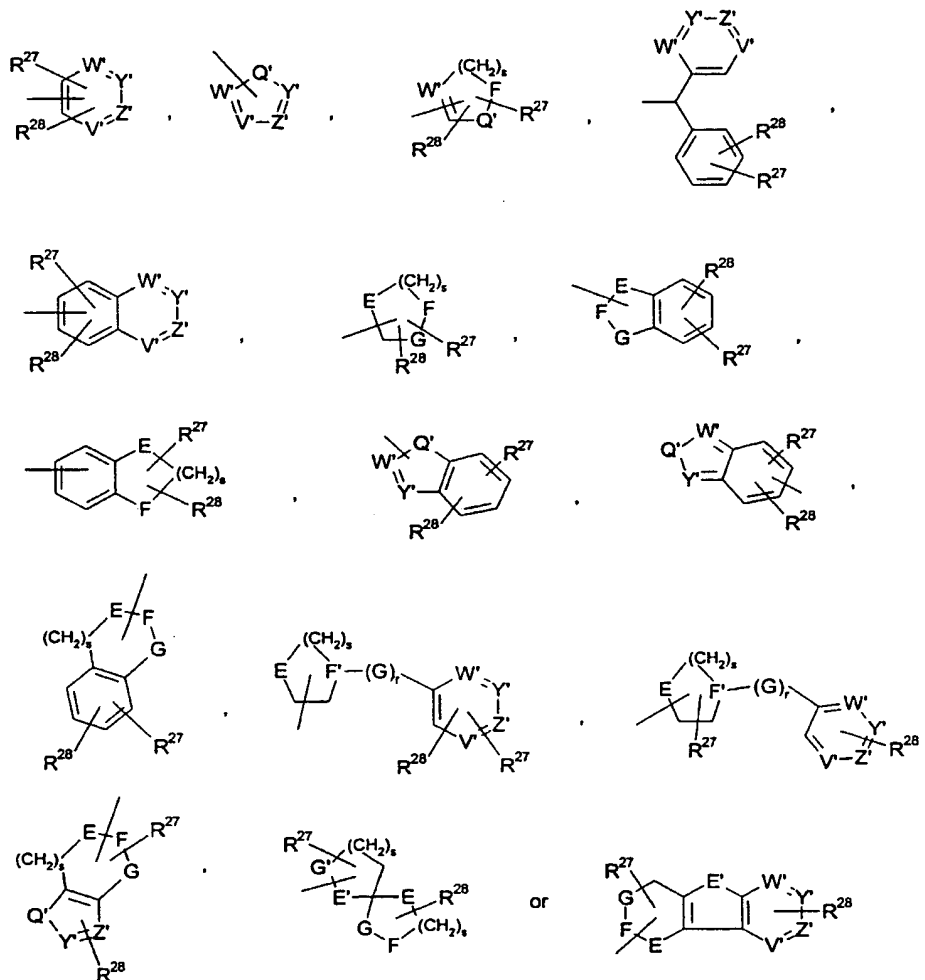
wherein  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $b$ ,  $c$ ,  $d$ ,  $p$  and  $q$  are as defined in claim 1.

- 5 29. A compound according to any one of the claims 26 to 28, wherein  $R^{5a}$  and  $R^{5b}$  independently are hydrogen, lower alkyl,  $-\text{OH}$ ,  $-(\text{CH}_2)_k\text{OR}^{6a}$ , aryl, aryl-lower alkyl,  $-\text{CH}_2\text{CF}_3$ ,  $-(\text{CH}_2)_g\text{-COOR}^{43}$ ,  $-\text{COOR}^{43}$ ,  $-(\text{CH}_2)_k\text{-CN}$  or  $-(\text{CH}_2)_k\text{-NR}^{6a}\text{R}^{6b}$  wherein  $g$ ,  $k$ ,  $R^{43}$ ,  $R^{6a}$  and  $R^{6b}$  are as defined in claim 1.
- 10 30. A compound according to claim 29, wherein  $g$  and  $k$  independently are 1, 2 or 3,  $R^{6a}$  and  $R^{6b}$  independently are hydrogen, lower alkyl such as methyl or ethyl, or aryl such as phenyl,
31. A compound according to any one of the claims 26 to 30, wherein  $R^{3a}$  and  $R^{3b}$  inde-  
 15 pendently are hydrogen, halogen,  $-\text{OH}$ ,  $-\text{O-lower alkyl}$ ,  $-\text{COO-lower alkyl}$ , lower alkyl or aryl-lower alkyl.

32. A compound according to any one of the claims 26 to 31, wherein  $R^{4a}$  and  $R^{4b}$  independently are hydrogen, -CN, -CONH<sub>2</sub>, -(CH<sub>2</sub>)-N(CH<sub>3</sub>)<sub>2</sub>, -O-lower alkyl, -CH<sub>2</sub>OH, -CH<sub>2</sub>O-aryl, -N(CH<sub>3</sub>)<sub>2</sub>, -OH, -CO<sub>2</sub>-lower alkyl or lower alkyl.

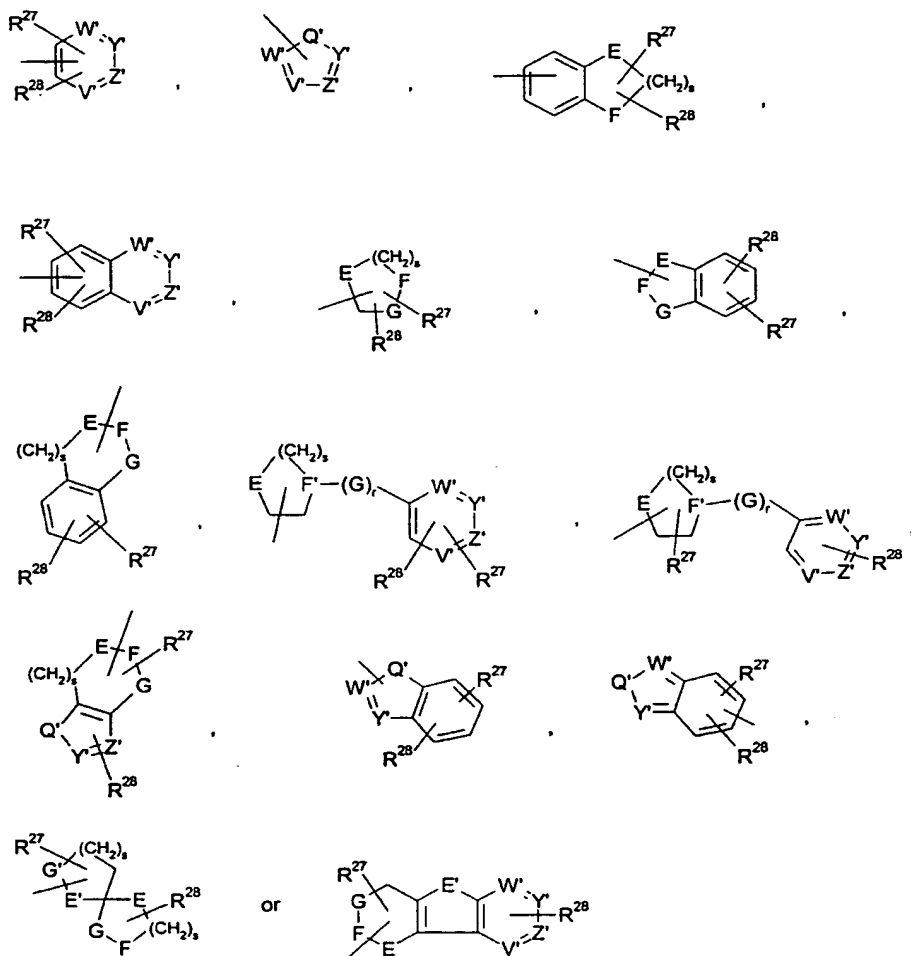
5

33. A compound according to any one of the preceding claims, wherein D is hydrogen,



10 wherein s, r, R<sup>27</sup>, R<sup>28</sup>, V', Y', Q', Z', W', E, E', F, F', G and G' are as defined in claim 1.

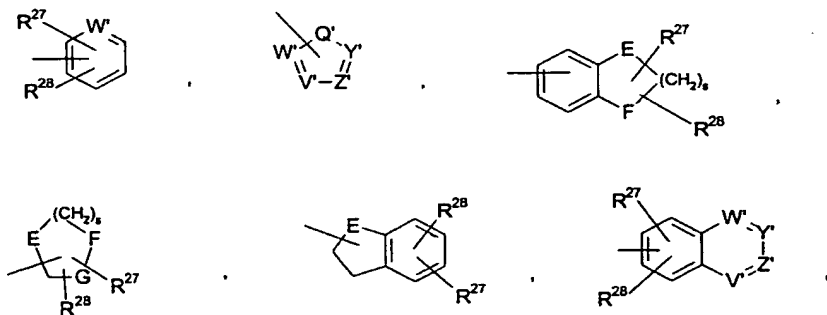
34. A compound according to claim 33, wherein D is hydrogen,

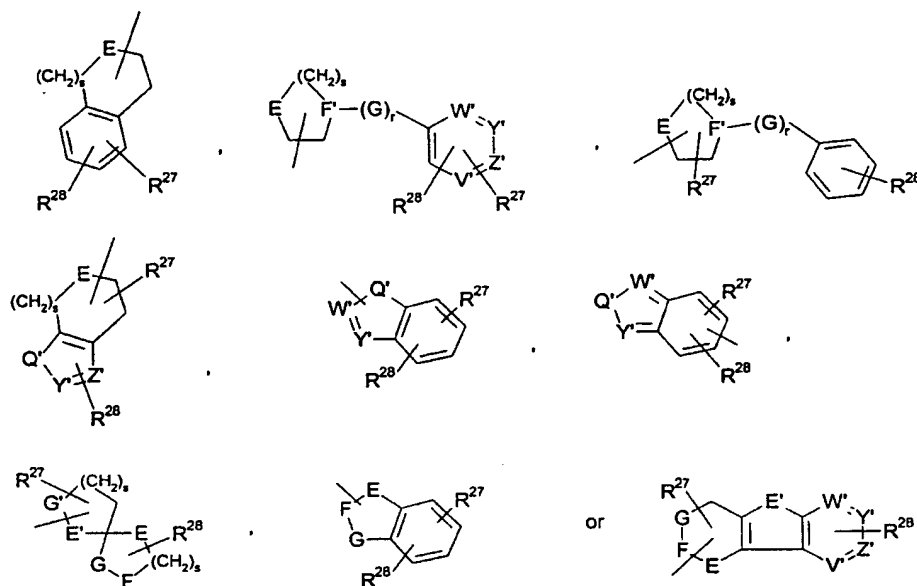


wherein  $s$ ,  $r$ ,  $R^{27}$ ,  $R^{28}$ ,  $V'$ ,  $Y'$ ,  $Z'$ ,  $Q'$ ,  $Z'$ ,  $W'$ ,  $E$ ,  $E'$ ,  $F$ ,  $F'$ ,  $G$  and  $G'$  are as defined in claim 1.

5

35. A compound according to claim 34, wherein  $D$  is hydrogen,





wherein E and E' independently are  $>\text{CHR}^{38}$ ,  $>\text{NR}^{39}$  or  $-\text{O}-$ ; F, G and G' independently are  $>\text{CHR}^{38}$ ,  $>\text{C}=\text{O}$  or  $>\text{NR}^{39}$ ; F' is  $>\text{CR}^{38}-$  or  $>\text{N}-$ ; and s, r,  $\text{R}^{27}$ ,  $\text{R}^{28}$ ,  $\text{R}^{38}$ ,  $\text{R}^{39}$ ,  $\text{V}'$ ,  $\text{Y}'$ ,  $\text{Z}'$ ,  $\text{Q}'$  and  $\text{W}'$  are as defined in claim 1.

36. A compound according to any one of the claims 33 to 35, wherein  $\text{R}^{27}$  and  $\text{R}^{28}$  independently are hydrogen; halogen such as  $-\text{Cl}$ ,  $-\text{Br}$  or  $-\text{F}$ ;  $-\text{CF}_3$ ;  $-\text{OCF}_3$ ;  $-\text{OCHF}_2$ ;  $-\text{OCH}_2\text{CF}_3$ ;  $-(\text{CH}_2)_y\text{NHCOCF}_3$ ;  $-\text{NHCOCF}_3$ ;  $-\text{CN}$ ;  $-\text{NO}_2$ ;  $-\text{COR}^{29}$ ,  $-\text{COOR}^{29}$ ,  $-(\text{CH}_2)_y\text{OR}^{29}$  or  $-\text{OR}^{29}$  wherein  $\text{R}^{29}$  is hydrogen, aryl or lower alkyl and y is 1, 2, 3 or 4; lower alkyl such as methyl, ethyl, 2-propenyl, isopropyl, tert-butyl or cyclohexyl; lower alkylthio;  $-\text{SCF}_3$ ; aryl such as phenyl;  $-(\text{CH}_2)_y\text{NR}^{29}\text{R}^{30}$  or  $-\text{NR}^{29}\text{R}^{30}$  wherein  $\text{R}^{29}$  and  $\text{R}^{30}$  independently are hydrogen,  $-\text{COO}$ -lower alkyl or lower alkyl and y is 1, 2, 3 or 4; or  $-\text{CONH}_2$ ; or  $\text{R}^{27}$  and  $\text{R}^{28}$  together form a bridge  $-\text{OCH}_2\text{O}-$ ;  $\text{R}^{38}$  is hydrogen;  $-\text{OCHF}_2$ ;  $-\text{OR}^{40}$  wherein  $\text{R}^{40}$  is hydrogen or lower alkyl; lower alkyl such as methyl, isopropyl or tert-butyl; lower alkylthio;  $-\text{SCF}_3$ ;  $-\text{CH}_2\text{OH}$ ;  $-\text{COO}$ -lower alkyl or  $-\text{CONH}_2$ ; and  $\text{R}^{39}$  is hydrogen, lower alkyl, aryl or aryl-lower alkyl.

37. A compound according to any one of the claims 1 to 36 for use as a medicament.

38. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 36 together with one or more pharmaceutically acceptable carriers or excipients.

39. A pharmaceutical composition according to claim 38 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 1 to 36.

40. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 36.

41. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 36.

42. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 1 to 36.

43. The method according to any one of the claims 40 to 42 comprising administering to a subject in need thereof an amount of the compound as defined in claim 1 to 36 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

44. Use of a compound according to any one of the claims 1 to 36 for the manufacture of a medicament for treating type I or type II diabetes.

45. Use of a compound according to any one of the claims 1 to 36 for the manufacture of a medicament for treating hyperglycemia.

46. Use of a compound according to any one of the claims 1 to 36 for the manufacture of a medicament for lowering blood glucose in a mammal.

47. A compound according to any one of the claims 1 to 36 characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay I or Glucagon

Binding Assay II disclosed herein corresponding to an  $IC_{50}$  value of less than 1  $\mu$ M, preferably of less than 500 nM and even more preferred of less than 100 nM.

**STATEMENT UNDER ARTICLE 19**

In order to delimit the present compounds from the documents cited in the International Search Report a new claim 19 has been added in which 9 disclaimers have been inserted. The compounds disclaimed are known from US 4,334,015, Table I, No11; US No 3,859,281, Example XVII (= US No 3,746,703, Example XVII = US No 3,836,580, Example XVII); and US No 5,229,038, Compounds 3 to 10.

Furthermore, new claims 20, 22 and 24, respectively, have been added in which R<sup>8</sup> has been restricted to halogen in meta-position.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 98/00287

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC6: C07C 243/18, C07D 209/04, A61K 31/15, A61K 31/40 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07C, A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CA, WPI		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5728646 A (NOBUHIDE TOMINAGA ET AL), 17 March 1998 (17.03.98) --	1-32
X	US 5229038 A (NOBUHIKO UCHINO ET AL), 20 July 1993 (20.07.93) --	1-32
X	EP 0451653 A2 (BAYER AG), 16 October 1991 (16.10.91) --	1-32
X	US 4334015 A (DEAN R. YARIAN), 8 June 1982 (08.06.82) --	1-32
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
7 October 1998		13-10- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer  Eva Johansson Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00287

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3859281 A (WILLIAM F. BRUCE), 7 January 1975 (07.01.75)  --	1-35
X	US 3836580 A (WILLIAM F. BRUCE), 17 Sept 1974 (17.09.74)  --	1-35
X	US 3746703 A (WILLIAM F. BRUCE), 17 July 1973 (17.07.73)  --	1-35
A	WO 9716442 A1 (MERCK & CO., INC.), 9 May 1997 (09.05.97)  -- -----	33-35, 40-43

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00287

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 36-39  
because they relate to subject matter not required to be searched by this Authority, namely:  
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☒ Claims Nos.: 1-17, 22-35 and 40-43  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claims 1-17, 22-35 and 40-43 are searched incompletely since these claims are so broadly formulated. It is not possible to carry out a meaningful search into the state of the art on the basis of these claims. For this reason the search has been limited to the examples and claims 18-21.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

27/07/98

International application No.  
PCT/DK 98/00287

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
US	5728646	A	17/03/98	JP 8310122 A	26/11/96
US	5229038	A	20/07/93	JP 4121717 A	22/04/92
EP	0451653	A2	16/10/91	AU 634047 B	11/02/93
				AU 7428091 A	17/10/91
				CA 2040018 A	12/10/91
				DE 4033808 A	17/10/91
				JP 4253967 A	09/09/92
				US 5185026 A	09/02/93
US	4334015	A	08/06/82	NONE	
US	3859281	A	07/01/75	US 3746703 A	17/07/73
				US 3836580 A	17/09/74
US	3836580	A	17/09/74	US 3746703 A	17/07/73
				US 3859281 A	07/01/75
US	3746703	A	17/07/73	US 3836580 A	17/09/74
				US 3859281 A	07/01/75
WO	9716442	A1	09/05/97	AU 1120897 A	22/05/97
				EP 0859771 A	26/08/98
				GB 9605158 D	00/00/00
				GB 9612062 D	00/00/00

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